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PROBLEMS IN SURGICAL ONCOLOGY

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THE SURGICAL CLINICS OF NORTH AMERICA

PROBLEMS IN SURGICAL ONCOLOGY

EDWARD J. BEATTIE, JR., M.D., *Guest Editor*

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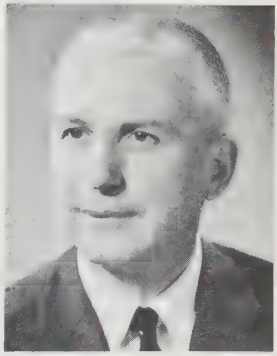
SYMPOSIUM ON PROBLEMS IN SURGICAL ONCOLOGY

Foreword



EDWARD J. BEATTIE, JR., M.D.

When this volume was first proposed to the publisher, there was proper concern that it might lack general interest. Since there are 600,000 new cancers annually in the United States, physicians and all surgeons should be well versed in oncology. It is equally true that surgical oncologists should be capable of optimal care of the cancer patient who may have another disease as well.

This volume is a compendium of important ideas and problems that have attracted the interest and attention of our Memorial Hospital surgeons and anesthesiologists. It contains, first, a brief explanation of our surgical philosophy in treating cancer. Then there are three papers by our anesthesia department. Dr. Howland points out that these papers reflect the magnitude of the physiologic support required for the patient undergoing radical surgery. The surgeon undertaking cancer surgery must be able to devote his entire attention to the anatomic problem and can be confident that the "anesthesiologist's half of the patient" is receiving equally expert care. A paper on massive blood transfusion reflects the result of 15 years of experience and investigation.

The paper on the energy mechanisms associated with glycolysis and the Krebs cycle is a step in the further understanding of both the mechanism of anesthesia and the methods that must be devised to treat the patient with hemorrhagic shock. Unexpected clotting problems during surgery have led to disaster because of lack of understanding of the mechanisms involved and the therapy indicated. We have attempted to evaluate this problem both with and without clotting laboratories. Before we began to use the thrombelastograph, the results were unsatisfactory. The thrombelastograph presents a simple and rapid method for determining clotting defects without the necessity for elaborate equipment and skilled technicians.

Cancer is the second commonest cause of death in the age group 2 to 16 years, trauma being first. About 6000 deaths per year in the United States occur in this age group, caused equally by leukemia-lymphoma and solid tumors. In the latter group, approximately half are nerve tumors. Two papers are presented citing our experience in childhood thyroid cancer and breast lesions in teenage girls.

There is a series of three papers concerned with the head and neck. The reports concern our experience with radiotherapy used preoperatively in radical neck dissection, our experience with a rather large series of bilateral simultaneous neck dissections (first done at Memorial Hospital), and a paper on the use of prostheses in covering stomas, prepared by our dental service.

The next paper concerns biopsy of the "normal" breast in treating breast cancer and is followed by a paper presenting some thoughts on breast reconstruction. We are not yet certain what role this reconstructive technique will play, but we recognize that if excision is to be the prime method of curing early breast cancers, reconstruction of this organ in some fashion is highly desirable.

The next paper discusses the need for thoracic and plastic cooperation in the treatment of major chest wall excision, and some rather extreme examples are given. These types of procedures should not be lightly undertaken. Our experience with the cancer patient who develops a lung shadow in his chest x-ray is presented next. All too frequently such patients are considered to have metastases and may not even be treated.

The status of renal cell cancer is followed by a paper concerning the treatment of bladder tumors. A discussion of management of gestational trophoblastic disease follows.

The next paper reports the role of radiotherapy in palliating colon cancer—a treatment too often neglected. Memorial Hospital data concerning melanoma are then presented. These data are important, since other treatment programs for melanoma must be compared with and evaluated in light of these results. The recent treatment of distressing lymphedema is discussed. The technique of using the omentum seems to be a valuable mode of therapy. The next paper concerns the protection of vascular grafts from infection by omentum. This technique appears to offer the surgeon a potential treatment in a situation otherwise hopeless or requiring an amputation.

There is a description of cryosurgery in the treatment of bone lesions. Cryosurgery affords valuable palliation of cancer and may well be a most important contribution to the treatment of some benign bone lesions. Whether cryosurgery, like radiotherapy, can induce sarcoma during treatment of benign bone lesions remains to be seen. Finally there is a paper summarizing our experience with pelvic exenteration and pointing out the indications and contraindications for this procedure.

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Philosophy of Cancer Care

EDWARD J. BEATTIE, JR., M.D.*

In the United States each year, approximately 3000 new cancers occur per million people. This totals almost 600,000 new cancers per year. It is estimated that approximately one third of the patients with potentially killing cancers are treated successfully; two thirds succumb from their disease. It is further estimated that with optimum care, by present day standards, half of the cancer patients might be salvaged, which would be a net gain per year of about 100,000 patients cured. This high incidence of cancer means that one of six persons will develop a cancer during his lifetime. Indeed, cancer is one of the major health problems of our country.

Only 84 years ago, patients with cancer were not admitted to general hospitals. Memorial Hospital for Cancer and Allied Diseases was founded in New York City in 1884 to care for unfortunate persons with cancer, who were considered outcasts from society, suffering from an unmentionable social disease. This reluctance to call cancer by its correct name persists today. There are many medical conditions more promptly fatal than cancer, but we as physicians are often extorted by relatives "not to tell him he has cancer." We agree that no one wants to know the grim, harsh facts of a relatively hopeless future. But trying to care for a patient who cannot understand why he is not promptly getting better from his disease, which is "positively not cancer," is a trying situation for the physician and the relatives alike. A factual, optimistic, and aggressive attitude by the physician is often the best cancer medicine. Besides, cancer is so protean and so often unpredictable that this approach is usually the most reasonable and the most accurate.

Over a century ago, the development of anesthesia, followed by the knowledge of antisepsis and asepsis, permitted the development of comfortable and relatively safe surgical operations. Surgeons throughout the world developed operations which began to cure certain types of cancer with reasonable success, such as breast cancer and colon-rectal cancer. Surgery has continued to be the best over-all method of treating cancer successfully. But it was soon recognized that cancers when first

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From the Department of Surgery

*Chairman, and Chief Medical Officer

seen were relatively far advanced and that too few patients were amenable to an attempt at surgical care. As it became increasingly obvious that surgery was successful only in the minority of the patients presenting themselves with cancer, other kinds of treatment were sought.

The discovery of radium and the development of ionizing radiation in the form of x-rays offered the second modality. Early attempts at radiotherapy were with relatively low energy and were found to be successful only when the lesion was superficial, such as in the skin, the cervix, and the oral cavity. Of importance, it was a method of treating cancer that had spread beyond the limits of surgical resection. It became apparent that radiotherapy, too, was controlling only a minority of the cancer problems. The era was soon characterized by disagreement and debate between proponents of surgery and of radiation therapy. A new group of patients developed, and a considerable number of these were ultimately admitted to Memorial Hospital; these were patients in whom radiation therapy had failed, but who still had lesions potentially amenable to surgical excision.

Gradually, cooperation between surgeons and radiotherapists developed. The cancer patient came to be treated by a combination of surgery and radiotherapy, with radiotherapy used either preoperatively or postoperatively. With the passage of time it became apparent that early cancers of the cervix and of the vocal cords could be relatively well controlled by radiation therapy, and that some cancers in these areas not controlled by radiotherapy could still be controlled with wide surgical excision.

Surgery was not standing still. The development of better anesthesia techniques, blood transfusions and blood banks, intravenous fluids, and antibiotics (which came in the late 1930's and early 1940's) set the stage for extended surgery.

There have been attempts to extend surgery to ever greater limits. One problem is to leave the patient with a satisfactory appearance, so that he will be presentable to society. The other problem is to restore function, so that the patient has a satisfactory quality of life and is not just "alive." Some advances have been made. Good orthopedic rehabilitation has made the loss of an extremity much less a catastrophe than heretofore. The use of colon or stomach to reconstruct the esophagus has made it possible for patients to swallow again who otherwise were doomed never to do so. The development of plastic surgical techniques has made more presentable many patients who by necessity have had to be subjected to extensive face, head, or neck surgery. Here the ravages of surgery are difficult to hide, compared to surgery done below the neck or inside the body. Extended radical surgery would be much more possible if organ transplantation were successful. The deterrent still is tissue rejection. Present medical means of controlling rejection are both immunosuppressive and carcinogenic, and thus need much extended study.

A new development after World War II was chemotherapy. This modality offered the first opportunity for the internist to treat cancer medically, at first for palliation and then with the hope of cure. The

search for the "magic bullet" was diligently pursued. For the most part chemotherapeutic agents had remarkable effectiveness in some (and even many) instances, but did not have satisfactory prolonged effects. But in the past two decades encouraging progress has been made. Burkitt's lymphoma, which is a "cancer" of the head and neck region in African children apparently caused by a virus, can be satisfactorily cured by effective use of chemotherapy, and it was discovered that the metastatic chorionepithelioma in the female, hopeless if treated by surgery or radiotherapy, could be cured by the use of chemotherapy. Lymphomas and leukemias, which had been promptly fatal, came under short-range control with some encouraging results. Recently, the first nontoxic chemotherapeutic agent, L-asparaginase, was developed and is presently under study. L-Asparaginase seems to have beneficial effects in two thirds of the acute lymphoblastic leukemias of childhood.

The fourth cancer "treatment," namely epidemiology and preventive medicine, has only recently been pursued. Knowledge that cancer could be an occupational disease stems from the descriptions of scrotal cancers of chimney sweeps in England, written by Sir Percival Pott in 1775. There have since been observations on the hazards of cancerogenesis from arsenic, radium, and coal tars. Much remains to be studied. There is wide discrepancy around the world in the incidence of cancer by organ systems. Japanese have a high incidence of cancer in the esophagus and stomach, but a low incidence in the colon and breast. Americans have a low incidence in the esophagus, but a high incidence in the breast and colon. The high and rising rate of lung cancer in the American male who smokes is a well-known fact. The difficulty in getting people to stop smoking cigarettes is too obvious for commentary.

The discovery by Papanicolaou that tumor cells can be found by cytologic examination gave an effective tool for earlier diagnosis and mass control of cancer. The greatest success has been in cancer of the cervix, where a routine Papanicolaou smear biannually from age 20 on should ultimately prevent women from dying of cervical cancer. Unfortunately, this knowledge is not universally applied, and there are many women dying unnecessarily from cancer of the cervix.

It is possible by the use of chest x-rays and sputum cytology twice yearly to diagnose a certain number of lung cancers at an early stage. In a small series of such patients at Memorial Hospital, it has been found that if the tumor can be found and localized by split cytologic studies at the time of bronchoscopy, by tomograms, bronchograms, or angiograms, the curability of lung cancer at this stage is approximately 65 per cent, in comparison to 40 per cent in "coin lesions" and a much lower percentage for more advanced cancers of the lung.

The modality for potential cancer treatment that presently needs exploration is immunotherapy. The real question is not that one person out of six develops cancer, but why five out of six never do. In experimental animals, there is evidence that cancers induced by chemical agents can produce antibody lymphocytes if injected into another animal. These antibodies can then suppress the growth of cancer if injected back into the original animal with the tumor. This mechanism needs greater

study, and the role of tumor antigens and tumor antibodies in man needs clarification. The possibility remains that cancer in man *is* virus induced, although except for the Burkitt's "lymphoma" virus, there has not yet been a virus recovered from human cancer.

It is apparent that the care of the cancer patient at present is a many-pronged, conjoint attack. Each patient needs careful study and evaluation. Every attempt should be made to control the disease and prolong life as long as the patient is comfortable and the quality of life is satisfactory. Heroic attempts to maintain life in the suffering, hopeless situation seem ill-advised. But great care must be taken that a situation be considered hopeless only when it is truly hopeless. It is obvious that the operability and resectability of a tumor will depend to a very great extent on the surgeon's skill and experience with that type of surgery, and that generalizations cannot be made which could be applied uniformly over a country as large as the United States. Palliative surgery, which is done to make the patient more comfortable or to live more comfortably for whatever time he has to live, is justified in carefully selected patients. It is wise that there be close cooperation in any given hospital among the surgeons, physicians, and radiotherapists interested in the cancer problem, so that they can render good advice, support, and help to each other. In no other field of medicine is it more important than that there be a close physician-patient and patient-family relation.

Follow-up of the cancer patient is equally important, though too frequently neglected by the medical profession. It is obvious that the patients who are not cured of cancer should be followed frequently, if for no other than humane reasons. Patients potentially cured need close observation. It is possible that local recurrences will occur or problems will arise which are still amenable to correction if found and treated early. It is also true that a rather high percentage of cured patients will develop new cancers. In studies at Memorial Hospital we have found that the cancer patient who is thought to be cured of cancer develops important new problems at the rate of approximately 7 per cent per year. This means that careful scrutiny in following the cancer patient for life is a *mandatory* part of cancer care. One must never fall into the trap of assuming that new cancers are metastases from unsatisfactorily treated former cancers.

Immediate and Delayed Mortality Associated with Massive Blood Transfusions

C. PAUL BOYAN, M.D.*

WILLIAM S. HOWLAND, M.D.**

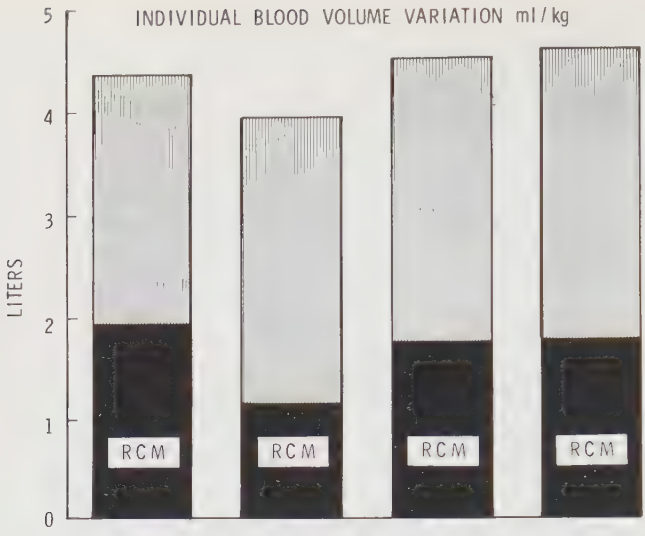
Blood loss is a major complication of radical surgery for cancer. Much has been learned during the past 10 years about the treatment of massive hemorrhage. Rapid reduction of effective circulating blood volume evokes widespread adjustment to the newly created dynamic state within the human body: redistribution of blood flow, translocation and changes in the make-up of fluid compartments, and altered neurohumoral responses. It is imperative to maintain adequate circulation and tissue perfusion during hemorrhage. The final goal is to return to homeostasis by qualitatively and quantitatively replacing all fluid losses. Red cells, plasma, and interstitial fluid are usually lost together, but in various proportions. The so-called "third space" can sequester large amounts of fluids which are not available for maintaining circulating blood volume, although they are still within the body. The time elapsed between blood loss and replacement and the status of hydration of the patient before surgery are factors to be reckoned with.

Thus it is difficult to make rules regarding blood and fluid replacement. Some patients can lose 25 per cent of their blood volume without any ill effects, while similar hemorrhage will put other patients in a state of hypovolemic shock. Diligent fluid replacement requires experience. It should be stressed that no single test or measurement will give the answer to what should be done and how to do it. Absolute values of many determinations can be misleading: they should be done serially and above all correlated with the over-all clinical picture. We should not treat separate signs and symptoms, but the patient as a whole. This cannot be stressed too strongly.

From the Department of Anesthesiology

*Formerly Chief of Clinical Service

**Chairman



	Preop 7-26-63	Postop 9000 ml Blood D-75 Fluids	Preop 7-24-64	Preop 1-25-65
wt / kg	43	43	55	60
BV	4.4	4.0	4.6	4.5
ml / kg	102	93	84	75
Hct	42	30	39	40

Figure 1. Correlation between blood volume and body weight over a period of 16 months, including an operation requiring 9000 ml. of blood and fluid replacement. The blood volume did not change much, while the ratio of blood (in ml.) to weight (in kg.) varied from 102 to 75.

Citrated bank blood, plasma expanders, and electrolyte solutions are good substitutes for lost blood and are readily available. Microhematocrit and blood volume determinations; electrocardiographic, central venous pressure, and pulse wave monitoring; blood transfusions under pressure—all have helped to increase the scope of blood replacement.

Massive blood transfusion is defined as a consecutive administration of 20 or more pints of bank blood in the operating and recovery rooms within less than 24 hours.

The following guidelines are observed by the members of the Department of Anesthesiology who take care of the blood and fluid replacement during surgery and postoperatively.

1. A blood volume determination preoperatively with ^{131}I-human serum albumin establishes the baseline for each patient. Adults probably have a blood volume norm for their vascular compartment, which cannot be defined in terms of milliliters per kilogram body weight (Fig. 1).[9] This may explain the diversity of normal values in the literature. Blood volume determinations are not reliable during acute bleeding. Poor mixing, leakage, and technical difficulties are responsible factors in variable results. But this test is helpful in assessing the adequacy of

fluid replacement after the circulation has been improved and the signs of shock have disappeared.

2. At least two large veins are cannulated preoperatively with large-bore plastic needles or cutdown catheters, thus providing avenues for rapid transfusion. For surgery in the pelvis and below the heart level, the veins of the arms or the jugular veins are used, to avoid loss of transfused blood in the operative field before it has passed through the heart. For surgery above the heart level, the veins of the legs are used.

3. The electrocardiogram of every patient has to be constantly monitored by oscilloscope. If there are signs of cardiac irritability, such as ventricular extrasystoles, immediate measures are instituted to remedy the situation. The monitoring of the pulse wave in one of the fingers is helpful in assessing the status of the peripheral perfusion. Interpretation of the pulse wave requires experience, because lowering of body temperature and prolonged pressure on the finger by the photocell can influence its configuration.

4. Serial microhematocrit determinations have proved to be of value in our hands during the treatment of massive hemorrhage.[6] High hematocrits, above 45 per cent, require an infusion of plasma, dextran, or crystalloid solutions, while figures below 30 per cent are an indication for whole blood transfusions. Readings between these two values have to be compared with the baseline, if available, and correlated with other clinical signs before the type of infusion is decided upon. This test is inexpensive, easy to do, and of great help.

5. Central venous pressure monitoring should be established in all patients in whom massive blood loss is anticipated.[7] A plastic needle in one of the jugular veins is the alternative route if one of the arm veins cannot be cannulated. Central venous pressure is basically a reflection of the right heart competence, rather than of blood volume. It has proved valuable in gauging the rapidity of fluid administration that will be tolerated by a given patient, thus preventing overtransfusion. Central venous pressure readings can be misleading, because a normal blood volume with a failing heart will give high readings, while impeded venous return will reduce the venous pressure.

6. Urine output is measured whenever possible, especially in abdominal operations. It is a simple and usually reliable test for total body hydration. An increase in the hourly urine output toward normal (40 to 60 ml.) is a good sign of the adequacy of fluid replacement. Normal kidneys will accommodate any inadvertent overhydration and restore the proper water balance.

7. Citrated blood, although the best available substitute for lost blood, is not the most physiological replacement. A unit of bank blood contains 450 ml. of whole blood and 67.5 ml. of ACD solution (formula A of the National Institutes of Health. The characteristics of such a unit of bank blood are compared with those of normal human blood in Table 1. In summary, the essential abnormalities of ACD preserved bank blood are: (1) low temperature; (2) low pH due to combination of metabolic and respiratory acidosis; (3) increased concentration of K, Na, lactate, pyruvate, and citrate; and (4) deficiency in Ca^{++}, platelets, and clotting factors V and VIII.

Our long experience with massive blood transfusions has established the following rules and observations:

1. Cold bank blood should be warmed to body temperature while being transfused to a patient who is in hemorrhagic shock or receiving a rapid blood transfusion (5 units or more per hour).[1] Infants and children should receive warmed blood only. If this is not done, the rapidly cooled heart could arrest.

2. The acid bank blood should be buffered with $NaHCO_3$ (7 to 8 mEq. per unit of blood) when given to a patient who is in hemorrhagic shock or receiving rapidly more than 2500 ml. of citrated blood.[5]

3. Patients receiving large amounts of bank blood should be well ventilated to avoid hypercarbia.

4. Patients with normal calcium metabolism, except infants, do not need the addition of calcium salts.[4] The body has a huge reservoir of calcium in the bones and can draw from it when the need arises. The combination of hypothermic heart and exogenous Ca^{++} can produce cardiac arrhythmia and cardiac arrest.

5. The citrate in the bank blood is easily metabolized through the Krebs cycle, and is not a problem in normothermic patients who have good tissue perfusion.[3]

6. Hyperkalemia in bank blood is mainly due to the outward migration of K^+ from the red cells during storage. K^+ re-enters the red cells when they are exposed to normal physiological conditions. We have not seen significant increase in potassium with massive blood transfusions.[5]

7. Five hundred ml. of fresh frozen plasma, containing all plasma clotting factors but platelets, should be given when the blood transfusion approaches 8 to 10 units. If there are signs, difficult to ascertain clinically, of bleeding tendency the administration of fresh frozen plasma is indicated.

8. Water and electrolyte balance should not be overlooked. The normal daily water requirements, 1.5 ml. per kg. per hour for adults, 3.0 for children, and 6.0 for infants, should be calculated and satisfied. Thus an adult who has had nothing by mouth since midnight and is operated on in the morning is already short of water by 500 to 1000 ml. The daily sodium chloride requirement is about 5 to 10 gm. in adults and can be replaced by normal saline. Our rule of thumb is that 10 ml. per kg. of half strength normal saline in 2.5 per cent distilled water for the first hour and then half of that amount per hour will cover the water and electrolyte needs in the average adult. Additional losses through exposed surfaces should be taken into consideration and replaced.

9. Surgery and manipulations of abdominal or thoracic viscera create a "third space" to which plasma or interstitial fluid are translocated. A transfusion of Plasmanate or Dextran-75 will replenish the plasma losses. Dextran-75 is not a qualitative replacement like Plasmanate or albumin, but stays in the cardiovascular compartment for at least several hours until the body can mobilize some of its stored proteins.[2]

10. A thrombelastogram provides a quick and readily available test for clotting deficiencies encountered during massive blood replacement.

Fibrinolysis and thrombocytopenia will require aminocaproic acid or platelet concentrate.

The following is an example of the calculation of blood and fluid replacement during radical surgery. The estimated blood loss during resection of a large sacral tumor was 11,000 ml. During the operation, which lasted 8 hours, the patient received 11,000 ml. of bank blood, D-75 1000 ml., Plasmanate 500 ml., fresh frozen plasma 500 ml., half-normal saline in 2.5 per cent dextrose 4000 ml., normal saline 1000 ml., and 600 ml. of Normosol, for a total of 18,600 ml. of fluids.

The operating room mortality was 11 per cent among 91 consecutive patients who received rapidly 20 or more units of bank blood in 4½ years. This low mortality was achieved by observing the guidelines for massive blood transfusions as previously described.

The three main factors responsible for these results are the warming to body temperature of the cold bank blood, the omission of Ca^{++}, and the administration of sodium bicarbonate. Buffering with sodium bicarbonate has been of vital importance where large amounts of bank blood were transfused, and particularly so in patients receiving rapidly 20 or more units of citrated blood, and it has reduced our previous mortality of 30 per cent to the present 11 per cent.

Of these 91 patients, 52 were anesthetized with diethylether, 3 of whom died in the operating room; 25 were anesthetized with halothane, and 5 of them died. The rest of the patients were anesthetized with cyclopropane (5 patients), methoxyflurane (5 patients), and sodium pentothal (4 patients), and 2 of the last group died during surgery. It is possible to compare only the mortality in the operating room between patients anesthetized with diethylether and with halothane. Those who died all received blood, an average of 29.2 (± 6.0) units. The halothane group had a mean age of 49.2 (± 6.8) years, received an average of 27.2 (± 3.9) units of bank blood, and all were good anesthetic risks; the diethylether group had a mean age of 64 (± 2.9) years and received an average of 32.3 (± 7.6) units of blood; 2 were good risks and 1 a fair anesthetic risk. The value of χ^2 for diethylether patients versus those anesthetized with halothane, all receiving rapidly 20 or more units of citrated blood, was 3.672, which approached significance at the 0.05 level (χ^2–3·841, $P<0.05$) and can be accepted as a meaningful difference. It also can be added that the patients who were anesthetized with ether were older, received more blood, and were not such good anesthetic risk as the halothane group. Thus we believe that patients receiving massive blood transfusions and anesthetized with diethylether have a better chance of immediate survival than those receiving halothane.

The over-all hospital mortality (0 to 300 postoperative days) among these 91 patients was 44 per cent. A further breakdown of the mortality gives the following figures:

In the operating room	11%	10 patients
24 hours after transfusion	5%	5 patients
7 postoperative days	7%	6 patients
30 postoperative days	13%	12 patients
In the hospital (up to 300 postoperative days)	8%	7 patients
	44%	40 patients

Table 1. *Characteristics of Citrated and Normal Blood*

	BANK BLOOD (ACD)	NORMAL
pH	6.65	7.40
Temperature (°C.)	4-6	38
Hematocrit (per cent)	41.6	45
Protein (per cent)	7.3	7-8
O_2 saturation (per cent)	35.3	98
Pco_2 (mm. Hg)	191	35-45
Standard HCO_3 (mEq per liter)	5	22-26
K (mEq. per liter)	7-21	4.5
Ca (mEq. per liter)	0.5	5.0
Lactate (mEq. per liter)	5.65	1.3
Pyruvate (mEq. per liter)	0.22	0.07
Citric acid (mEq. per liter)	11.0	0.15
Sodium (mEq. per liter)	170.0	140.0
Platelets (per cu. mm.)	0	240,000
Factors V and VIII (per cent of normal)	50	100

The hospital mortality of the 67 patients in this study who received 20 to 29 pints of blood was 33 per cent, while for those who received 30 units or more it was 75 per cent. The mean age of the 40 patients who died in the hospital was 53 (± 14) years and for the ones who were discharged it was 45.8 (± 13.3) years. Seventeen patients of those who died in the hospital had a preoperative blood pressure of 160/60 mm. Hg or higher, while in the discharged group there were 8 patients in this category. The difference between the two groups is statistically significant ($p<0.005$).

Assessment of anesthetic and surgical risk is notoriously inaccurate. There are multiple factors which increase patient morbidity and mortality. Because of the lack of data as to which of these factors contribute to the hazards of anesthesia and surgery, it is impossible to deny any patient the chance for surgical cure.

REFERENCES

1. Boyan, C. P.: Cold or warmed blood for massive blood transfusions. Amer. Surg., *160*: 282 (Aug.), 1964.
2. Boyan, C. P., Underwood, P. S., and Howland, W. S.: The effects of operation, anesthesia and plasma expanders on blood viscosity. Anesthesiology, 27:279 (May-June), 1966.
3. Howland, W. S., Bellville, J. W., Zucker, M., Boyan, C. P., and Cliffton, E. E.: Massive blood replacement. V. Failure to observe citrate intoxication. Surg. Gynec. Obstet., *105*: 523 (Nov.), 1957.
4. Howland, W. S., Schweizer, O., and Boyan, C. P.: Massive blood replacement without calcium administration. Surg. Gynec. Obstet., *118*:814 (April), 1964.
5. Howland, W. S., Schweizer, O., and Boyan, C. P.: The effect of buffering on the mortality of massive blood replacement. Surg. Gynec. Obstet., *121*:777 (Oct.), 1965.
6. Jacobs, R., Howland, W. S., and Goulet, A.: Serial micro-hematocrit determinations in evaluating blood replacement. Anesthesiology, 22:342 (May-June), 1961.
7. Ryan, G. M., and Howland, W. S.: An evaluation of central venous pressure monitoring. Anesth. Analg., *45*:754 (Nov.-Dec.), 1966.
8. Schweizer, O., and Howland, W. S.: Potassium levels, acid-base balance and massive blood replacement. Anesthesiology, 23:735 (Nov.-Dec.), 1962.
9. Underwood, P. S., and Howland, W. S.: Serial blood volume determinations associated with major cancer surgery. Anesth. Analg., *45*:797 (Nov.-Dec.), 1966.

Some Metabolic Changes Associated with Anesthesia and Operation

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The metabolic effects of anesthesia and operation are important from the standpoint of acid-base balance and the energy mechanisms associated with aerobic cellular respiration. Although hemorrhagic shock is the most frequently mentioned cause of excess lactate production and metabolic acidosis, other factors may be responsible for significant changes in acid-base balance and certain aspects of anaerobic and aerobic intermediary carbohydrate metabolism. The present study was undertaken to evaluate the etiologic importance of these factors in the metabolic disturbances occurring during major operations.

SOURCE OF MATERIAL

The study was conducted on 332 adult patients subjected to all types of major operations except neurologic, cardiovascular and obstetric. The only contraindication to inclusion in the study was the presence of known metabolic disease. After induction of anesthesia with thiopental, the patients were intubated and maintained in light planes with ether, halothane-nitrous oxide-oxygen or thiopental-nitrous oxide-oxygen. Succinylcholine or d-tubocurarine chloride provided the necessary relaxation. Fluid replacement with physiologic saline, blood, or plasma expanders was employed as indicated. Transfused blood was warmed after the third unit. In the majority of cases 44.6 mEq. of sodium bicarbonate was administered after every fifth unit of blood.

Acid-base balance and glucose, lactate, and pyruvate levels were obtained on every patient. In addition to these basic studies, two groups within the series were evaluated for parameters related to the tricarboxy-

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lic acid cycle. Blood levels of citrate, α-ketoglutarate, and malate were determined in 125 patients. A second group of 100 patients was studied primarily from the standpoint of parameters related to the energy mechanisms associated with aerobic carbohydrate metabolism, namely, inorganic phosphate, adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP). Levels of ATP were also obtained for 93 other patients in the series.

METHOD

Arterial blood samples were obtained anaerobically from the brachial or femoral artery just prior to induction of anesthesia, at intervals during operation, and at the end of the procedure. The samples were analyzed immediately for hematocrit, P_AO_2, oxygen saturation, pH, P_ACO_2, standard bicarbonate, actual bicarbonate, total carbon dioxide, glucose, lactate, pyruvate, citrate, α-ketoglutarate, malate, ATP, ADP, AMP, and inorganic phosphate. The Astrup technique[12] was employed for acid-base levels. Oxygen tension was determined by a Po_2 electrode, type E5044, and thermostatic cell, type D615, attached to the Radiometer, and oxygen saturation by the American Optical Company's oximeter. Enzymatic methods[1] were employed for pyruvate, lactate, α-ketoglutarate, malate, ATP, ADP, and AMP levels. Citric acid values were obtained by the method described by Pincus, as modified by Elliott.[3] Excess lactate was calculated from Huckabee's formula.[4]

RESULTS

The total series of 332 cases was divided into two main groups. The first group of 232 cases excluded the 100 patients studied for energy mechanisms. Analysis of the group was directed primarily to an evaluation of lactate production and its effect on acid-base balance. For this purpose the group was subdivided into three categories based on the total lactate level at the end of operation: (1) minimum—less than 3 mEq. per liter; (2) median—3 to 5 mEq. per liter; and (3) maximum—more than 5 mEq. per liter. Excess lactate formation paralleled the total lactate, with levels of 0.300, 0.846, and 2.080 mEq. per liter, respectively. There were 159 patients in the group with lactate < 3, 48 with lactate 3 to 5, and 25 with lactate > 5 mEq. per liter. In the minimal lactate category, 65 patients were anesthetized with ether, 69 with halothane, and 25 with thiopental. The relative numbers of ether, halothane, and thiopental anesthesias were 37, 9, and 1 in the median category and 23, 2, and 0 in the maximum. Mean blood replacement was 969 ml., 2761 ml., and 3880 ml., respectively, in the three groups. Nineteen of the 232 patients were in severe hemorrhagic shock. These included 2 in the minimal lactate group (0.01 per cent), 10 in the median group (21 per cent) and 7 in the group with lactate > 5 mEq. per liter (28 per cent). In the latter category the mean total and excess lactate values for the 18 patients with no clinical evidence of shock (6.90 ± 1.28 mEq. per liter, with excess lactate 2.57 mEq. per liter) were comparable to those

of the 7 shock patients (6.01 ± 1.17 mEq. per liter, with excess lactate 2.00 mEq. per liter).

Table 1 gives the mean of the difference between the preoperative and end of operation samples, plus or minus the standard error of the mean, for hematocrit, several parameters of acid-base balance, lactate, and pyruvate in the two categories of patients with high lactate levels. Oxygen saturation and P_AO_2 were normal throughout. In the absence of buffering with sodium bicarbonate (top of Table 1), a direct relationship existed between the increase in the level of lactate and the decrease in standard bicarbonate and total carbon dioxide. The bottom of Table 1 reveals the salutary effect of sodium bicarbonate on the metabolic phase of acid-base balance.

The second main group (193 cases) included all patients in the series with ATP determinations. This group was studied from two standpoints: (1) the effect of anesthetic agents on various parameters of glycolysis and aerobic carbohydrate metabolism, and (2) the relationship of arterial lactate and ATP levels.

In this group 84 patients were anesthetized with ether, 84 with halothane–nitrous oxide–oxygen and 25 with thiopental–nitrous oxide–oxygen. There were 110 male and 83 female patients with an age range from the second to the ninth decade. The majority of patients were in the sixth and seventh decades. Procedures included 60 head and neck operations, 2 thoracic, 97 abdominal, 5 extremity, and 29 superficial. The mean blood replacement was 780 ml. with ether, 720 ml. with halothane, and 648 ml. with thiopental. Duration of operation was comparable with each of the three agents. No clinical evidence of shock was found in any patient.

Table 1. *The Mean of the Difference Between Preoperative and Postoperative Blood Samples in Four Groups of Patients*

	NO SODIUM BICARBONATE	
	Lactate 3 to 5 mEq. per liter (30 patients)	*Lactate > 5 mEq. per liter (14 patients)*
Hematocrit	− 1.20 ± 0.60	− 1.92 ± 0.74
pH	− 0.004 ± 0.012	− 0.05 ± 0.01 ($p < 0.001$)
P_Aco_2 (mm. Hg)	− 4.98 ± 2.41	− 5.06 ± 2.77
Standard HCO_3 (mEq. per liter)	− 2.23 ± 0.37 ($p < 0.001$)	− 4.63 ± 0.55 ($p < 0.001$)
Total CO_2 (mEq. per liter)	− 3.64 ± 0.86 ($p < 0.001$)	− 6.15 ± 1.08 ($p < 0.001$)
Pyruvate (mEq. per liter)	+ 0.14 ± 0.02 ($p < 0.001$)	+ 0.19 ± 0.03 ($p < 0.001$)
Lactate (mEq. per liter)	+ 2.31 ± 0.16 ($p < 0.001$)	+ 5.16 ± 0.38 ($p < 0.001$)
	WITH SODIUM BICARBONATE	
	Lactate 3 to 5 mEq. per liter (18 patients)	*Lactate > 5 mEq. per liter (11 patients)*
Hematocrit	− 1.33 ± 0.91	+ 0.27 ± 1.18
pH	+ 0.07 ± 0.01 ($p < 0.001$)	+ 0.045 ± 0.017
P_Aco_2 (mm. Hg)	− 5.27 ± 1.89 ($p < 0.02 > 0.01$)	− 2.60 ± 2.49
Standard HCO_3 (mEq. per liter)	+ 2.02 ± 0.47 ($p < 0.001$)	+ 1.44 ± 0.84
Total CO_2 (mEq. per liter)	+ 0.75 ± 0.67	+ 0.63 ± 1.27
Pyruvate (mEq. per liter)	+ 0.12 ± 0.02 ($p < 0.001$)	+ 0.22 ± 0.04 ($p < 0.001$)
Lactate (mEq. per liter)	+ 2.67 ± 0.19 ($p < 0.001$)	+ 4.86 ± 0.42 ($p < 0.001$)

Table 2. *The Mean of the Difference Between Preoperative and Postoperative Blood Samples, Including Parameters of Metabolism*

	ETHER (84 PATIENTS)	HALOTHANE-N_2O-O_2 (84 PATIENTS)	THIOPENTAL-N_2O-O_2 (25 PATIENTS)
Hematocrit	−2.13 ± 0.38 ($p < 0.001$)	−2.29 ± 0.36 ($p < 0.001$)	−1.68 ± 0.80
pH	+0.029 ± 0.009 ($p < 0.005 > 0.001$)	−0.005 ± 0.008	−0.018 ± 0.018
P_ACO_2 (mm. Hg)	−9.37 ± 1.14 ($p < 0.001$)	−3.28 ± 0.99 ($p < 0.005 > 0.001$)	−0.36 ± 2.26
Standard HCO_3 (mEq. per liter)	−2.25 ± 0.21 ($p < 0.001$)	−1.71 ± 0.21 ($p < 0.001$)	−1.54 ± 0.28 ($p < 0.001$)
Total CO_2 (mEq. per liter)	−4.69 ± 0.37 ($p < 0.001$)	−2.65 ± 0.35 ($p < 0.001$)	−1.76 ± 0.55 ($p < 0.005 > 0.001$)
Glucose (mg. per 100 ml.)	+56.22 ± 2.99 ($p < 0.001$)	+42.08 ± 3.40 ($p < 0.001$)	+55.04 ± 8.54 ($p < 0.001$)
Pyruvate (mEq. per liter)	+0.075 ± 0.009 ($p < 0.001$)	+0.034 ± 0.005 ($p < 0.001$)	+0.012 ± 0.007
Lactate (mEq. per liter)	+1.710 ± 0.179 ($p < 0.001$)	+0.316 ± 0.091 ($p < 0.001$)	+0.358 ± 0.149
Citrate (mEq. per liter)	+0.275 ± 0.076 ($p < 0.005 > 0.001$)	+0.519 ± 0.105 ($p < 0.001$)	+0.210 ± 0.065 ($p < 0.005 > 0.001$)
α-Ketoglutarate (mEq. per liter)	−0.0001 ± 0.003	+0.0003 ± 0.003	+0.012 ± 0.006
Malate (mEq. per liter)	+0.017 ± 0.012	+0.009 ± 0.007	+0.012 ± 0.006
ATP (mEq. per liter)	−0.025 ± 0.018	−0.013 ± 0.017	−0.033 ± 0.023
ADP (mEq. per liter)	−0.009 ± 0.003	−0.009 ± 0.003	
AMP (mEq. per liter)	−0.002 ± 0.000	−0.001 ± 0.001	
Inorganic phosphate (mEq. per liter)	+0.039 ± 0.125	−0.079 ± 0.093	

Table 3. *Effect of Lactate Level on ATP Level**

	NO OF CASES	LACTATE (mEq. per Liter)	ATP (mEq. per Liter)
Lactate < 3 mEq. per liter	154	+ 0.349 ± 0.050 ($p < 0.001$)	− 0.008 ± 0.012 ($p < 0.60 > 0.50$)
Lactate > 3 mEq. per liter	39	+ 3.215 ± 0.219 ($p < 0.001$)	− 0.073 ± 0.025 ($p < 0.01 > 0.005$)

*The mean of the differences between preoperative and postoperative blood samples, plus or minus the standard deviation of the mean.

The effect of the three anesthetic agents on hematocrit, acid-base balance, and various parameters of anaerobic and aerobic intermediary carbohydrate metabolism are shown in Table 2. Oxygen saturation and oxygen tension were normal throughout. There were no major differences in hematocrit or acid-base balance between ether, halothane, and thiopental. Significant elevation of glucose level occurred with all three agents. The only statistically significant change in the components of the Krebs cycle, including the energy mechanisms, was found in the citrate level, which was elevated in all groups.

The major variation between the three agents occurred in the values of lactate and pyruvate. Thiopental produced only a minimal elevation of pyruvate. Although statistically significant, the pyruvate increase with halothane was less than with ether. Similar but more marked variations distinguished the lactate levels of the three agents. Mean excess lactate was 0.944 mEq. per liter for ether, 0.157 for halothane, and 0.414 for thiopental.

Table 3 shows the relationship of lactate level to the arterial blood level of adenosine triphosphate. No significant diminution of ATP occurred until lactate attained values higher than 3 mEq. per liter.

DISCUSSION

The data in this report provide three main fields for discussion: (1) the effect of anesthetic agents on several parameters of glycolysis and aerobic carbohydrate metabolism; (2) the etiology of high lactate levels during operation; and (3) the relationship of significant elevations of lactate to acid-base balance and energy mechanisms.

From the standpoint of intermediary carbohydrate metabolism, the major points of similarity between the three anesthetic agents, ether, halothane, and thiopental, were the significant elevation of glucose and citrate levels and the minimal changes in α-ketoglutarate, malate, inorganic phosphate, ATP, ADP, and AMP. The sympathomimetic action of ether is an adequate reason for increased glucose production with this agent. Another explanation must be sought in the case of halothane and thiopental, since these agents lack adrenergic activity. Although the glucose content of ACD solution might be implicated, Schweizer and Howland[8] found that halothane produced a significant increase in glucose in the absence of transfusion. It is theoretically possible that

halothane and thiopental could exert a depressant effect on glycolysis, either through a reduction in supplies of inorganic phosphate or ADP (Pasteur effect) or by interference with the glycolytic enzymes. Enolase, which catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate (the last step in glycolysis preceding pyruvate formation) is inhibited by sodium fluoride. It is conceivable that a fluorinated hydrocarbon, halothane, might exhibit similar activity.

Since previous investigation by Schweizer and Howland[8] has failed to show elevation of citrate levels in the absence of blood replacement, the increase in citrate in the present study can be attributed to the citrate content of ACD solution. Lack of significant variation in levels of α-ketoglutarate, malate, inorganic phosphate, ATP, ADP, and AMP seems to indicate that the three anesthetic agents have little effect on aerobic metabolism in patients not in shock.

The major difference between ether, halothane, and thiopental occurs in the levels of pyruvate and lactate, and excess lactate. The authors have shown previously[6, 7] that inadequate tissue perfusion with resultant cellular hypoxia accounts for a large share of the excess lactate production. The adrenergic action of ether accentuates this situation. In the case of halothane and thiopental, excess lactate accounts for the major part of the increase in total lactate. This is not true of ether. Subtraction of the mean excess lactate of 0.780 mEq. per liter from the total increase in lactate of 1.71 mEq. per liter leaves a residual of 0.930 mEq. per liter of aerobic lactate, which cannot be explained on the basis of tissue hypoxia. Olson[5] and Boxer and Devlin[2] have suggested several mechanisms for lactate production in the presence of adequate tissue oxygenation. These include uncoupling of oxidative phosphorylation, blockage of ADP uptake by mitochondria, or interference with the glycerophosphate or acetoacetate-B-hydroxybutyrate shuttle systems for the transfer of electrons from extramitochondrial NADH to the intramitochondrial phosphorylating electron transport chain. It is theoretically possible that ether might activate one or more of these mechanisms, with resultant mandatory reduction of pyruvate to lactate to provide sufficient oxidized NAD^+ for continued flow of carbon through the glycolytic pathway.

Elevation of lactate level may be attributed to several factors. In the present series, the major cause of significantly increased lactate was inadequate tissue perfusion. The highest levels of excess lactate were found in the groups with lactate levels > 3 mEq. per liter. These two groups also contained 17 of the 19 cases of hemorrhagic shock. In addition, the 18 non-shock patients in the group with lactate > 5 mEq. per liter showed levels of lactate and excess lactate comparable to those of the 7 shock patients in the same category. This indicates the probable presence of undetected hypovolemia. The patients with high lactate levels received the largest volume of blood transfusion. Since bank blood preserved with ACD solution contains large amounts of lactate and pyruvate, the volume of blood replacement can be a significant contributory factor to the total lactate. A third factor is the anesthetic agent. In the median and maximum lactate groups the percentage of ether anesthesia was, respectively, 77 and 92 per cent. We have shown

that ether produces higher levels of total lactate and excess lactate than the other two agents in the series. Additional factors may be the length and variety of operation and the type of fluid replacement therapy. The maximum duration of operation occurred in the high lactate category. Since saline was the sole fluid therapy aside from blood and plasma expanders, the role of dextrose solutions cannot be evaluated. In a recent study,[11] the authors have shown that Ringer's lactate solution does not contribute significantly to the level of blood lactate.

High lactate levels do not necessarily carry a poor prognosis. In a series of 42 patients with lactate levels over 5 mEq. per liter, Schweizer and Howland[10] showed that lactate values between 5 and 10 mEq. per liter had no permanent deleterious effect provided that the oxygen tension and oxygen saturation were within the normal range and that the clinical situation was amenable to appropriate therapy. The prognosis was poor when total lactate was higher than 10 mEq. per liter. In the present series the only fatality was a patient who expired 1 hour after operation from uncontrollable hemorrhage.

The effect of elevated lactate levels on acid-base balance is shown in Table 1. The data in this series and in a previous study indicate that lactic acid is the primary factor in producing depression of the levels of standard bicarbonate and total carbon dioxide during operation. Although citric acid values rise with massive blood replacement, the effect on the metabolic status of the patient is minimal in comparison with lactate. Changes in phosphate and metabolites of the Krebs cycle are insignificant.

An important factor is the relationship of lactate levels to the energy mechanisms associated with aerobic carbohydrate metabolism. Each mole of lactate production involves the removal of one mole of a three-carbon unit from terminal oxidative metabolism. The end result is the loss of 15 mole equivalents of high-energy phosphate. Table 3, based on the 193 patients in group 2, indicates that lactate > 3 mEq. per liter does have a moderately significant depressant effect on the arterial blood levels of adenosine triphosphate. Unfortunately, ATP levels were not obtained on the series of patients in group 1 with lactate levels > 5 mEq. per liter. Although arterial blood levels of ATP are not necessarily indicative of tissue levels, the data suggest that elevated lactate levels may have a significant effect on energy storage. This could be an important factor in the metabolic changes associated with shock.

SUMMARY AND CONCLUSIONS

Acid-base balance and several parameters related to anaerobic and aerobic carbohydrate metabolism were studied in a series of 332 adult patients subjected to major operations exclusive of cardiovascular, obstetric, and neurologic procedures. One hundred seventy-six patients were anesthetized with ether, 130 with halothane–nitrous oxide–oxygen, and 26 with thiopental–nitrous oxide–oxygen. Arterial blood samples were obtained immediately prior to operation, at intervals during operation, and at the end. The samples were analyzed immediately for hematocrit, acid-base balance, glucose, lactate, pyruvate, and excess lactate

in all patients. In addition, values for citrate, α-ketoglutarate and malate were determined in 125 cases; inorganic phosphate, ADP, and AMP in 100; and ATP in 193 patients in the series.

For analytical purposes the series was divided into two groups. The first group of 232 included all patients except the 100 studied primarily for energy mechanisms. The second group consisted of the latter 100 patients plus 93 patients with ATP determinations from the first group.

In the first group the end lactate level was < 3 mEq. per liter in 159 patients, 3 to 5 mEq. per liter in 48, and > 5 mEq. per liter in 25. Excess lactate paralleled total lactate values. The major causes of significantly elevated lactate levels were cellular hypoxia subsequent to inadequate tissue perfusion (including 19 cases of hemorrhagic shock), massive blood replacement and ether anesthesia.

High lactate levels are important from two standpoints: (1) effect on acid-base balance, and (2) relation to energy mechanisms associated with the tricarboxylic acid cycle.

In the present series increase in the level of lactate was the major factor in producing depression of standard bicarbonate and total carbon dioxide values during operation. Other acids, including citrate, played a minor role. Patients with diabetes mellitus or renal failure were not included in the series. Lactate levels > 3 mEq. per liter were associated with a moderately significant decrease in arterial blood levels of ATP. Although the blood level is not indicative of the tissue level of ATP, the data suggest that markedly elevated lactate levels may interfere with energy storage mechanisms. This could be important in shock.

Ether, halothane, and thiopental all produced a statistically significant increase in glucose levels. Although elevated glucose levels with ether can be explained on the basis of adrenergic glycogenolysis, halothane and thiopental lack sympathomimetic action. It is theoretically possible that these agents may exert a depressant effect on glycolytic enzymes, with resultant elevated glucose levels associated with low lactate and pyruvate values. With the exception of citrate, none of the agents produced significant changes in the metabolites of the aerobic Krebs cycle, inorganic phosphate, ATP, ADP, or AMP levels. Increased citrate values were associated with blood replacement.

The only major differences between the agents occurred in the levels of total and excess lactate and pyruvate. Ether produced significantly greater amounts of total and excess lactate than halothane or thiopental. The lactate increase with the latter two agents was due almost entirely to excess lactate production. In the case of ether, excess lactate accounted for only half the total increase in lactate, leaving a large residual aerobic lactate for which there are only theoretical explanations.

REFERENCES

1. Bergmeyer, H. V.: Methods of Enzymatic Analysis. New York, Academic Press, 1963.
2. Boxer, G. E., and Devlin, T. M.: Pathways of intracellular hydrogen transport. Science, *134*:1495, 1961.
3. Elliott, K. A. C.: Intermediary metabolites and respiratory catalysis. Physiol. Rev., *21*: 267, 1941.

4. Huckabee, W. E.: Relationship of pyruvate and lactate during anaerobic metabolism. I. Effects of infusion of pyruvate or glucose and of hyperventilation. J. Clin. Invest., 37:244, 1958.
5. Olson, R. E.: "Excess lactate" and anaerobiosis. Ann. Int. Med., 59:960, 1963.
6. Schweizer, O., and Howland, W. S.: Metabolic changes associated with hemorrhagic shock. Anesth. Analg., 43:420, 1964.
7. Schweizer, O., and Howland, W. S.: Significance of lactate and pyruvate according to volume of blood transfusion in man. Ann. Surg., 162:1017, 1965.
8. Schweizer, O., Howland, W. S., Sullivan, C., and Vertes, E.: The effect of ether and halothane on blood levels of glucose, pyruvate, lactate and metabolites of the tricarboxylic acid cycle in normotensive patients during operation. Anesthesiology, 28:814, 1967.
9. Schweizer, O., Howland, W. S., and Sullivan, C.: Effect of thiopental–nitrous oxide–oxygen anesthesia on blood levels of glucose, pyruvate, lactate and metabolites of the tricarboxylic acid cycle during operation. Anesthesiology, 29:208, 1968.
10. Schweizer, O., and Howland, W. S.: Prognostic significance of high lactate levels. Anesth. Analg., 47:383, 1968.
11. Schweizer, O., Howland, W. S., and Vertes, E.: Effect of lactated Ringer's solution on glycolysis. Anesth. Analg., 47:737, 1968.
12. Siggaard Anderson, O., Engel, K., Jorgensen, K., and Astrup, P.: A micro method for determination of pH, carbon dioxide tension, base excess and standard bicarbonate in capillary blood. Scand. J. Clin. Lab. Invest., 12:172, 1960.

Clotting Problems During Surgery

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The most commonly encountered clotting problems during surgery are fibrinolysis and defects associated with massive transfusion. Less frequent problems include congenital deficiencies of clotting factors, platelet depression secondary to chemotherapy or tumor replacement of the marrow, factor deficiencies caused by liver disease, platelet deficiencies associated with uremia, anticoagulated patients, and clotting defects associated with extracorporeal bypass.

Clotting defects in the operating room are most simply understood if one first understands that there are presently available only three emergency therapeutic agents—that is, agents that act immediately: fresh frozen plasma for plasma coagulation factor deficiencies; platelet concentrates for platelet deficiencies; and epsilon-aminocaproic acid for fibrinolysis. Heparin might also be included as "emergency" therapy for disseminated intravascular clotting.

We have therefore approached clotting defects in the operating room from the standpoint of the therapy that is available: therapy for factor deficiencies, platelet deficiency, and fibrinolysis.

DEFICIENCY STATES

When treating plasma factor deficiencies, it should be noted that only three clotting components are considered "labile"—that is, easily destroyed by storage or common bank blood techniques: factors V and VIII and platelets. Therefore specially prepared plasma (fresh frozen plasma) or blood (fresh blood) is not necessary unless a deficiency of these factors exists, or unless the deficiency is so severe that "concen-

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trates" are needed to reach minimum hemostatic levels without overloading the patient's cardiovascular system. Primary plasma factor deficiencies which are severe enough to require factor concentrates are rare and would presumably cause symptoms severe enough to be noted preoperatively (congenital afibrinogenemia, classical hemophilia). It should be noted, however, that a negative bleeding history does not preclude a surgically significant clotting disorder, as deficiencies which are not severe enough to cause spontaneous bleeding may still be troublesome during surgery. In addition, minor deficiencies of multiple factors may cause bleeding, even when the deficiencies are mild enough to be insignificant if occurring alone.

Fresh frozen plasma will, therefore, help *any* plasma coagulation factor deficiency, since it preserves factors V and VIII as well as the "stable" plasma factors. The "stable" factors include factors II, VII, IX, X, XI, and XII. Factor XIII, a recently discovered factor, is responsible for clot stabilization and when deficient causes *late* (postoperative) bleeding. There are no factors presently designated IV or VI, though calcium is sometimes called factor IV. Factor III is the thromboplastin released from injured tissues, and factor I is fibrinogen.

Platelet deficiencies (whether thrombocytopenic or thrombocytopathic) require platelet transfusions. Fresh whole blood is a poor substitute for platelet concentrate, as few platelets are added when the dilutional factor is taken into account. Fresh whole blood which still contains platelets is becoming more difficult to obtain as more and more blood banks adopt the practice of separating the blood components as soon as the blood is drawn. *All* platelet deficiencies benefit by platelet transfusion with the exception of idiopathic thrombocytopenic purpura, in which the patient's immune system rapidly destroys all platelets, whether his own or transfused, so that preoperative corticoids, followed by splenectomy, form the only effective therapy.

It might be mentioned at this time that plasma factor deficiencies of the vitamin K dependent factors (II, VII, IX, X) should be treated with fresh frozen plasma, as intravenous vitamin K does not even begin to work until 4 hours after its administration.

SPECIFIC DEFICIENCY STATES

Our most frequent problem is the clotting defects which may occur with massive blood transfusion. The problem of bleeding during massive blood replacement is complicated by the fact that after sufficient bleeding and replacement have occurred, the factors lacking in bank blood (factors V and VIII and platelets) contribute to the bleeding. To prevent deficiency of factors V and VIII during and after massive blood replacement, 500 ml. of fresh frozen plasma is routinely given after every 10 units of transfused bank blood.

Thrombocytopenia following massive transfusion has been reported by many investigators. However, it has been difficult to correlate abnormal bleeding during surgery with this thrombocytopenia. In a group of patients studied at Memorial Hospital, it was found that although

there was a drop in platelets after the tenth unit of blood, we encountered few levels below 100,000 platelets per cu. mm., well above the so-called minimum hemostatic level of 70,000. Some patients with platelet counts even below 70,000 do not bleed excessively, so that there is no real arbitrary minimum hemostatic level. Because of the relative scarcity of platelet concentrates, and our low incidence of significant platelet depression after massive transfusion, we do not give prophylactic platelet transfusions during massive blood replacement. It would seem to be the opinion at the present time that the thrombocytopenia observed during and after massive transfusion is on a dilutional basis, and that there is no definable level of platelets below which patients will bleed.

We have seen no bleeding disorders caused by low calcium levels, even as low as 5 mg. per 100 ml. We no longer give supplemental calcium during massive transfusion.

Incompatible blood transfusion is described as being accompanied by thrombocytopenia, hypofibrinogenemia, decreased factors V and VIII, prolonged prothrombin time, and fibrinolysis, and it is probably one of the consumption coagulopathies. The diagnosis of this condition under general anesthesia is very difficult; our incidence of transfusion reactions under general anesthesia has been surprisingly low, considering the number of blood transfusions that are given to cancer patients undergoing surgery.

Another problem which may be encountered is platelet depression secondary to chemotherapy or bone marrow involvement with tumor. A platelet transfusion is the appropriate therapy for surgery, as in the preoperative preparation of patients with leukemia. All patients who have received chemotherapy should have a platelet count immediately prior to surgery and after any dilution of platelets by preoperative blood transfusions has taken place.

Patients with uremia may bleed excessively, largely due to abnormal platelet factor 3. This platelet malfunction is not reflected in the platelet count.

Hemorrhagic phenomena and bleeding are common during surgical operations in patients with liver disease. The coagulation defect in liver disease is multiple, involving platelets, prothrombin formation, and factors V, VII, and X. Four of the recognized clotting factors in human plasma, prothrombin (factor II) and factors VII, IX, and X, require vitamin K for their formation. Vitamin K is absorbed from the gastrointestinal tract only in the presence of bile salts and normal bacterial flora and is then utilized by the body in the formation of the vitamin K–dependent coagulation factors. A prolonged prothrombin time is therefore found in obstructive jaundice, as well as in cirrhosis, severe acute hepatitis, and tumor replacement of the liver. Bleeding may occur when the prothrombin time is above 20 to 25 seconds (control 13). Fresh frozen plasma is the most rapid therapy for this deficiency. As mentioned previously, intravenous vitamin K does not even begin to have an effect for 4 hours, and should be started 2 days preoperatively.

Thrombocytopenia is common in the presence of portal hypertension. Moreover, in many patients with chronic liver disease, the clotted blood

lyses more rapidly than normal. Often the fibrinolytic activity is too weak to account by itself for hemorrhagic symptoms, but it may potentiate other coagulation defects.

Patients undergoing extensive hepatic resections present particular problems. Both pre-existing coagulation defects, due to the liver disease, and acquired defects from massive blood replacement and trauma to the liver are encountered. After removal of large portions of the liver, prothrombin and factor VII fall to less than 40 per cent within 4 days. Factor V does not fall as low, but the decrease occurs more rapidly. Hypofibrinogenemia occurs in some patients, but levels return to normal by the first postoperative day. Platelet counts decline rapidly in all patients, which may be a dilutional effect secondary to massive blood replacement, Fibrinolysis may also occur and cause, or potentiate, abnormal bleeding.

Patients who are receiving anticoagulants may not have their clotting defect reversed prior to surgery, as in patients who are having pulmonary emboli. These patients are usually receiving heparin, which acts to prevent clotting by affecting many factors. Heparin impairs clotting in the early stages by interfering with the formation of thromboplastin. It is thought to inactivate factor IX by forming a reversible complex, thus inhibiting thromboplastin generation. It may also interfere with thrombin formation in the latter stages of clotting. If given intravenously, heparin acts almost instantaneously. Heparin produces a prolonged whole blood clotting time. [Only if the clotting time is below 20 minutes will a one-stage prothrombin time determination be accurate and remain useful in evaluating simultaneous heparin and coumarin therapy.]

The effects of heparin may be reversed by the administration of protamine sulfate. Protamine forms a stable salt with heparin. Since protamine has anticoagulant properties of its own, it should not be given in excess, and the dosage should be varied according to the length of time since heparin was last administered. We give 1 mg. protamine for every milligram of heparin administered, or 0.5 mg. per milligram of heparin if 2 hours have elapsed since the last dose. Intravenous heparin lasts from 3 to 5 hours, intramuscular heparin for 12 hours. The length of action depends upon the initial dose. Oral heparin is ineffective.

Patients with chronic embolic disease are usually on coumarin. The coumarin drugs are nearly all structurally similar to vitamin K and depress the formation of those clotting factors which require this vitamin for their synthesis (factors II, VII, IX, and X), but in varying degrees and sequence. This anticoagulant probably acts as a competitor for the site of action of the vitamin. Salicylates may augment the action of the coumarin-like drugs, as may propylthiouracil, antibiotics (by depressing intestinal flora), and some testosterone derivatives. Salicylates alone may have an anticoagulant effect.

The effect of the coumarin-like drugs may be reversed by the intravenous administration of 50 to 100 mg. of vitamin K_1. A response to safe levels will take longer, obviously, than if the defect is corrected with fresh frozen plasma. The vitamin K_1 should be continued until the prothrombin time is normal. The more slowly produced coagulation

factors (VII, IX, X) may not return to normal for 2 days. If emergency surgery is indicated, or if significant bleeding occurs, fresh blood or plasma should be administered to correct the coagulation defects.

FIBRINOLYSIS AND CONSUMPTION COAGULOPATHIES

In addition to deficiency states, fibrinolysis may also cause bleeding during surgery and is caused either by the release of fibrinolysins (as in prostatic cancer) or by disseminated intravascular coagulation (the hypercoagulable state), which is followed by compensatory fibrinolysis.

Lysis occurs as a normal homeostatic mechanism and may increase with various stimuli without the patient exhibiting abnormal bleeding. However, when significant fibrinolysis does occur, the clinical picture is usually quite striking, the surgical wound visibly and abruptly oozing or "weeping." There remains no doubt that significant fibrinolysis occurs during surgery and anesthesia, especially surgery of the chest (as in pleurectomies) and surgery associated with prostatic cancers.

The treatment of fibrinolysis caused by the release of excessive amounts of circulating lysins is epsilon-aminocaproic acid. Though reports of cerebral or coronary thromboses are in the literature, we have seen no adverse results with the use of doses under 20 gm. per 24 hours. The best results seem to be obtained with continuous, slow infusion of 5 gm. of EACA (usually in 150 ml. of normal saline), after a rapidly administered initial dose of 5 gm.

Fibrinolysis will improve with EACA, if the release of lysins is primary, or anticoagulation, if the fibrinolysis is a compensatory mechanism "triggered" by generalized intravascular clotting. Fibrinolysis which occurs as a compensatory mechanism for intravascular clotting may be aggravated by the administration of EACA, however. Combined intravascular clotting and fibrinolysis are seen with obstetrical accidents, pulmonary emboli, incompatible blood transfusion, and other conditions. Such patients show hypofibrinogenemia and reduced levels of factors I, II, V, and VIII, as well as platelets (their clotting components are being consumed). Treatment in these cases should be directed at the intravascular clotting, as the fibrinolysis is a compensatory mechanism. Anticoagulation, usually partial, should arrest this type of clotting defect, as may the administration of dextran. Since dextran causes no increased bleeding when given to patients with normal clotting, it probably "anticoagulates" by diluting the already partially consumed clotting factors. It would seem obvious that in severe deficiencies, the consumed factors should be replaced as the intravascular clotting is reversed (fresh frozen plasma for factor deficiencies, platelet transfusion for platelet deficiency, and fibrinogen if its level falls below 100 mg. per 100 ml.).

Virtually all of the coagulation difficulties occurring during obstetric accidents reveal low fibrinogen levels. This has been referred to as the Defibrination syndrome. Again, there are also low levels of factor V, factor VIII, and platelets.

Bleeding problems during and subsequent to the use of extracorporeal circulation vary considerably. As heart-lung machines have

improved technically, certain problems have definitely decreased and others vary from clinic to clinic. Generally, bleeding associated with extracorporeal circulation also varies with the duration of the bypass; the longer the bypass, especially those over 2 hours, the greater the incidence of coagulation defects. Coagulation defects that occur during extracorporeal circulation can be due to thrombocytopenia, overheparinization, overdose of the heparin antagonist (protamine), destruction of fibrinogen, fibrinolysis, and depression of factors V and VIII. In a number of cases, pre-existing defects can be demonstrated. These abnormalities may not disturb normal clotting, but during and after cardiac bypass these changes may be magnified (the additive effect of multiple minor deficiencies), resulting in overt bleeding.

The thrombocytopenia that occurs with extracorporeal circulation is due to the removal of damaged platelets from the circulation. Some of these platelets have lost their viability after collection and during use in the machine. The largest drop in platelets occurs in the first few minutes of bypass, with a more gradual decrease coming about as the perfusion continues. The return of platelets to normal levels may require up to 24 hours. It must be remembered that during and after cardiac surgery large amounts of stored blood may have to be administered, and this can also result in a thrombocytopenia by means of dilution.

Severe fibrinogen loss occurred with the traumatic, early, experimental pump-oxygenators. The hypofibrinogenemia may be due to fibrinogenolysis or intravascular clotting or both. It has been observed by some workers that there is hypercoagulability of the blood and intravascular clotting if heparinization is less than excessive during cardiac bypass. This is probably because even under normal conditions, excess amounts of heparin are necessary to prevent the clotting of blood which has been exposed to foreign surfaces. The balance preventing intravascular clotting during extracorporeal circulation is easily upset. We usually give 3 mg. of heparin per kg. of body weight (or more, as needed) before instituting bypass.

After administration of the calculated dose of protamine at the end of the bypass (milligram for milligram, allowing for heparin metabolism if the bypass has been long), occasional instances of recurrence of bleeding have been reported. Various reasons have been proposed as the cause of this "heparin rebound." At the present time many authors believe that this phenomenon is due to an overdose of protamine, which has anticoagulant properties of its own, but the etiology of this renewed bleeding is by no means clear.

EVALUATING BLEEDING IN THE OPERATING ROOM

The need for a simple, objective method of evaluating "excessive" bleeding in the operating room has never been adequately met. Technically feasible tests (which can be performed in the operating suite without specialized personnel) have proved notoriously unreliable (e.g., glass clotting time, with visual estimation of fibrinolysis) or slow (e.g., evaluation of clot retraction). The problem is compounded by the fact

that most clotting laboratories are not open in the evenings or on weekends; even when they are open, obtaining test results may take too long to be of much help in emergency therapy.

We have been evaluating the thrombelastograph, using whole blood instead of citrated plasma, as previously reported, for simple, rapid diagnosis of clotting disorders. The thrombelastograph is a mechanical-optical system in which the blood sample is placed into a metal cup. A steel cylinder, attached to a torsion wire, is lowered into the metal cup, which is slowly oscillating (Fig. 1). As the clot forms, the cylinder becomes attached to the oscillating cup by way of the fibrin strands. The oscillations of the cylinder are then transmitted to a mirror attached to the torsion wire. The mirror reflects a fixed light source into two scales, one a direct visual read-out, the other a reel of photographic film. Since each sample uses at least 30 cm. of photographic film, and each reel is 15 meters long, manual plotting of the deflections is necessary in order to get an immediate recording, thus tying up one person for 30 minutes or more. A photosensitive strip was therefore attached to the thrombelastograph, so that a plot is obtained via a direct writer as clotting occurs. One sample at a time can be recorded in this fashion.

In our operating rooms, we are looking only for significant clotting disorders that can be promptly corrected by therapy. Since there are, as previously mentioned, really only three emergency therapeutic agents, we have attempted to diagnose only these clotting deficiencies. The three available therapeutic agents are: (1) fresh frozen plasma, for plasma coagulation factor deficiencies; (2) epsilon-aminocaproic acid, for

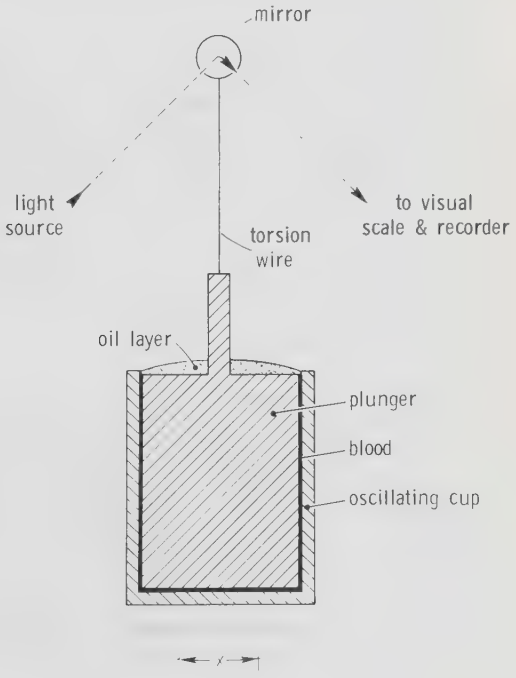

Figure 1. Diagrammatic representation of the thrombelastograph.

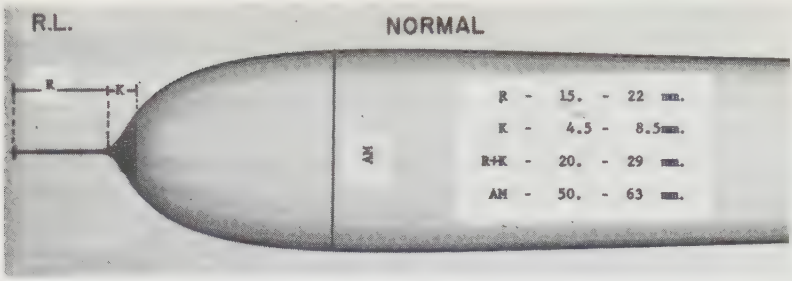

Figure 2. Normal thrombelastographic tracing and values.

fibrinolysis (with and without hypercoagulability); and (3) platelet concentrates, for platelet deficiencies. Fibrinogen is also available, but since the vast majority of significant fibrinogen deficiencies occur in "obstetric accidents" and there is no obstetrics department in our hospital, we have virtually no indication for its use.

We are, therefore, looking for only three major areas of clotting deficiencies, specific and quantitative diagnoses being left until later. If there is a plasma coagulation factor deficiency (or the patient is anticoagulated) the time necessary for inititiation of clot formation will be prolonged. This is expressed as *R*, and normally the clot should begin to form between 7½ and 11 minutes after being drawn. (This appears as a 1 mm. deflection in each direction starting between 7½ and 11 minutes.) The speed with which the clot develops, once it has started, will be normal unless the deficiency is very severe. The clot should reach a total amplitude of 20 mm. (10 mm. deflection in each direction) in 10 to 14½ minutes after being drawn. This is expressed as $R + K$. If there is a deficiency of platelets or fibrinogen, the clot will not become substantial in size, the size being expressed as *AM*. The clot should attain a minimum total amplitude of 50 mm. (25 mm. deflection in each direction).

Clot retraction can also be observed, but this is a slow process—a gradual, mild decrease in the amplitude of the clot over a period of hours. The rapid differential diagnosis of fibrinogen versus platelet deficiency requires addition of reagents or further testing (e.g., a fibrinogen level or platelet count). If fibrinolysis is present, the clot will form and then disappear. A normal clot configuration is shown in Figure 2.

Method

All blood samples are drawn through a needle whose minimum gauge is 18. Several milliliters of blood are drawn and discarded (to rid the test sample of intravenous fluid or tissue thromboplastin) and a fresh syringe is then attached to the needle to collect the specimen. Whenever possible, samples are drawn through plastic needles (either central venous or peripheral) and samples are always drawn into plastic syringes, because plastic is believed to activate clotting less rapidly than glass. If the sample is difficult to obtain (slow to aspirate, etc.), another venipuncture is done. A stopwatch is started as the sample is being drawn and the specimen is placed in the thrombelastograph *within* 5

minutes, as recorded by the stopwatch. A thin covering of mineral oil is placed over the top of the blood sample in the cup, to prevent drying at the blood/air interface.

One relevant difference in technique from that used by clotting laboratories is that these blood samples are not drawn into tubes or syringes which contain an anticoagulant. This is whole blood, as it comes from the patient, with no chance for fibrinolysis to be reversed by the presence of an anticoagulant.

Once the blood sample has been placed in the thrombelastograph, three records are kept of the clot formation: (1) manual plotting; (2) simultaneous automatic recording, via the photosensitive strip and direct read-out recorder; and (3) photographic recording. Lee-White clotting times were also determined and the clots observed (incubated in a 37° C. water bath) for retraction and fibrinolysis.

The only technical aspects which require care are avoidance of using blood obtained from an arduous venipuncture and the necessity of absolute cleanliness of the steel cup which holds the sample.

Results

Many types of clotting disorders have been recorded, some previously diagnosed, some with concomitant tests by the clotting laboratories,

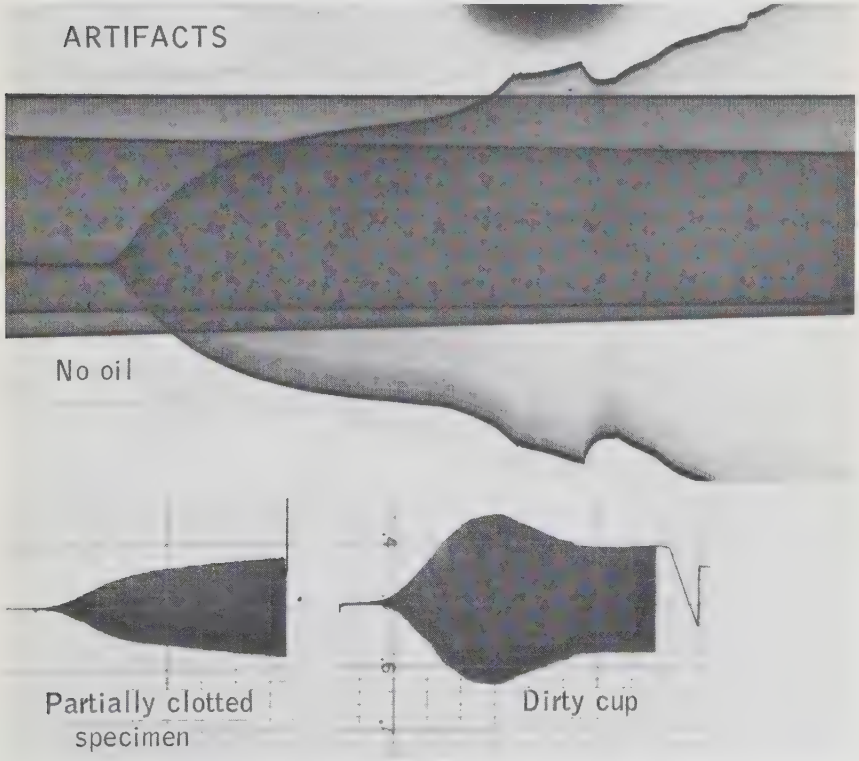

Figure 3. Artifactually abnormal thrombelastographic tracings.

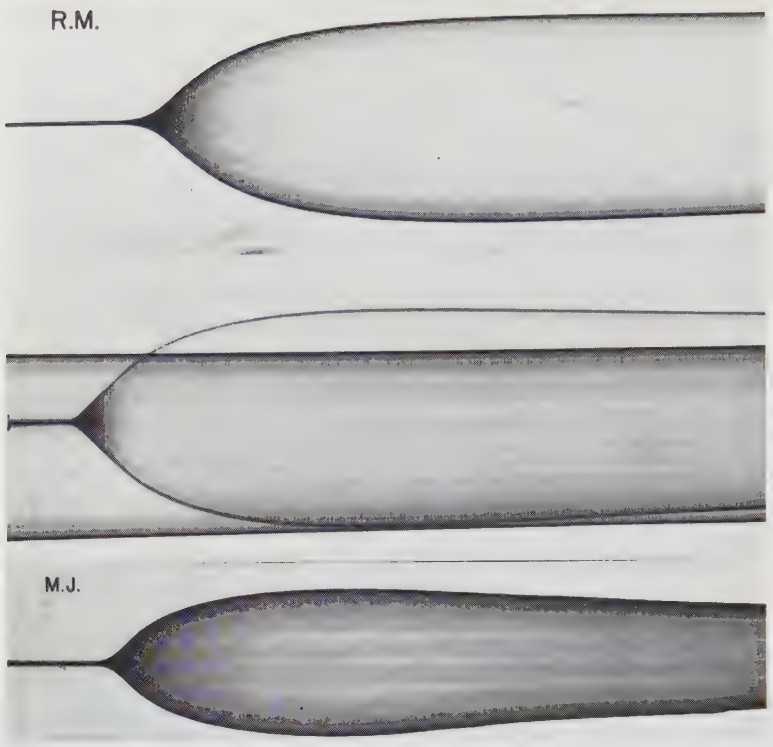

Figure 4. Plasma coagulation factor deficiencies. *Top*, Rosenthal's disease; *Middle*, Rosenthal's disease after therapy; *Bottom*, patient receiving coumarin therapy.

some previously unsuspected. Figure 2 shows a normal clot and the normal values for R, $R + K$, K and AM. In thrombelastograph terminology, the elapsed times (in minutes) are multiplied by two except for the AM (maximum amplitude), which is the sum of the maximum deflection on either side of the zero point. For instance, if the clot reaches 1 mm. oscillations on either side of the zero point 8 minutes after venipuncture, $R = 16$; if the clot reaches 10 mm. oscillations on either side of the zero point at 12 minutes, $R + K = 24$. K is determined by subtracting R from $R + K$. Figure 3 shows artifacts which may be encountered: (1) no oil placed on top of the specimen, allowing the clot to dry out; (2) a specimen which was partially clotted before being placed in the thrombelastograph (mimicking a consumption coagulopathy); and (3) a specimen placed in an improperly cleaned cup (mimicking fibrinolysis).

Several plasma factor deficiencies have been recorded. The top tracing in Figure 4 is typical of this type of deficiency, showing the delay in initiation of clot formation ($R = 40$). The top tracing is that of a patient with known Rosenthal's disease (factor XI deficiency). She had a history of bleeding after tooth extractions and for 8 days postpartum; during a previous breast biopsy excessive bleeding had necessitated the administration of fresh frozen plasma (though since factor XI is considered

to be stable, regular stored plasma should have corrected her deficiency). Studies from the coagulation laboratory showed abnormal glass clotting time (22′37″ to 47′), abnormal partial thromboplastin time (213 seconds, control 69 seconds), and abnormal thromboplastin generation time (which was corrected by serum and plasma). Platelet count and prothrombin time (one stage) were normal; there was no lysis and no circulating anticoagulants were found. The middle tracing in Figure 4 shows the correction of the factor deficiency after administration of 500 ml. of fresh frozen plasma (*R* now is 20). After administration of the fresh frozen plasma, the patient underwent a breast biopsy without the occurrence of unusual bleeding.

The bottom tracing in Figure 4 also shows a plasma factor deficiency, but this time caused by coumarin therapy in a patient being treated for thrombophlebitis. The *R* value is 46 at a time when the patient's one-stage prothrombin time was 30 seconds (control 13).

Figure 5 shows the typical appearance of platelet deficiency. This patient had idiopathic thrombocytopenic purpura, with a history of easy bruising and vaginal bleeding. Petechiae were noted on physical examination. The morning she had her splenectomy, her platelet count was

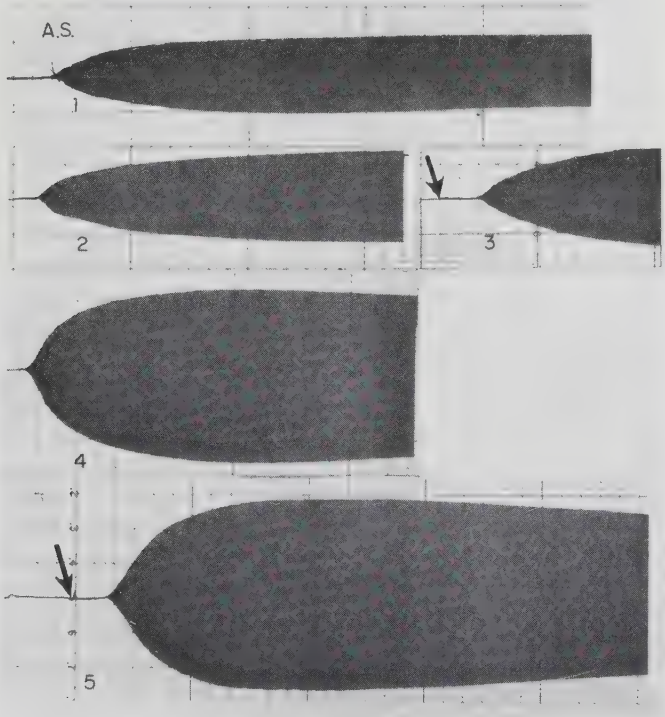

Figure 5. Platelet deficiency (idiopathic thrombocytopenic purpura). *1*, Before splenectomy; 2, immediately after splenectomy; 3, after 2 units of blood and 250 ml. of fresh frozen plasma; 4, after platelet transfusion; 5, one day post operation.

Figure 6. Fibrinogen deficiency.

16,000 (the top tracing in Fig. 5) and the thrombelastograph *AM* was only 22. She had had little response to a corticoid prep, perhaps because she had been on long-term steroids for rheumatoid arthritis. Other laboratory tests revealed glass clotting time of 10′10″; bleeding time of 1′06″; prothrombin time 14.4 seconds (control 13); fibrinogen 255 mg. per 100 ml.; and a positive Rumpel-Leede test. There was little bleeding until the specimen was removed (second tracing, Fig. 5, in which *AM* was 24), at which time some bleeding occurred from gastric arteries, necessitating a transfusion of 2 units of bank blood. After transfusion, and in the recovery room, persistent bleeding was noted. Two hundred fifty ml. of fresh frozen plasma was given prophylactically (third tracing, Fig. 5), with subsequent slight improvement in the width of the clot (*AM* was 30), while awaiting preparation of a platelet transfusion (to tide the patient over until she could form her own platelets). After an 8-unit platelet transfusion, her clot improved significantly (*AM* rose from 30 to 50), as shown in the fourth tracing in Figure 5, and by the following morning, her clot was within normal range (*AM* was 58), as the patient's own platelets became viable (fifth tracing in Fig. 5).

One of the advantages of thrombelastographic monitoring is demonstrated by the above case: the ease of obtaining frequent samples and their results, as the clinical course progresses.

As mentioned previously, platelet deficiency cannot be differentiated from severe fibrinogen deficiency without obtaining a fibrinogen level. Figure 6 is the tracing of a 17-year-old girl with multiple cavernous hemangiomas. She was being operated upon for prenuptial excision of a large vulvar hemangioma. No serious clotting defect had been demonstrated by routine preoperative screening tests (bleeding time, clotting time, prothrombin time, and platelet count). The thrombelastograph tracing showed a markedly diminished maximum amplitude of 18. Further laboratory tests were done during surgery and revealed a fibrinogen level of 30 mg. per 100 ml., platelet count of 20,000, prothrombin time of 17.8 seconds (control 13.4), and partial thromboplastin time of 102 seconds (control 69), and there was little clot retraction with large fallout. Extensive further testing, including individual factor assays, revealed a continually low fibrinogen level, low-normal platelet count, slightly low factor V, and detectable fibrinogen breakdown

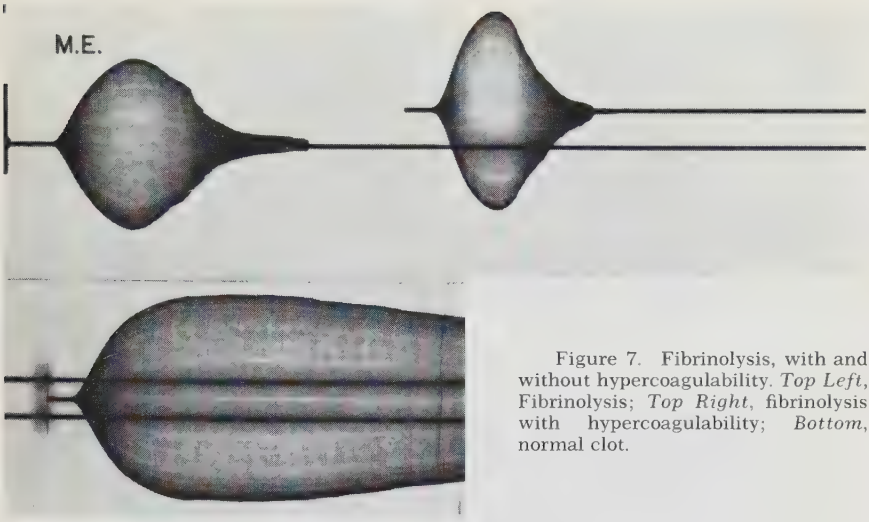

Figure 7. Fibrinolysis, with and without hypercoagulability. *Top Left*, Fibrinolysis; *Top Right*, fibrinolysis with hypercoagulability; *Bottom*, normal clot.

products, all of which led to the diagnosis of continuous consumption coagulopathy, associated with her multiple cavernous hemangiomas.

Another example of so-called consumption coagulopathy is shown in Figure 7, in this case iatrogenically induced by general anesthesia and surgery (pleurectomy for metastatic breast carcinoma). This patient exhibited fibrinolysis (lysis beginning after 19 minutes) during surgery, as shown in the first tracing, and then went on to demonstrate hypercoagulability (the initiation of clot formation was too rapid, as evidenced

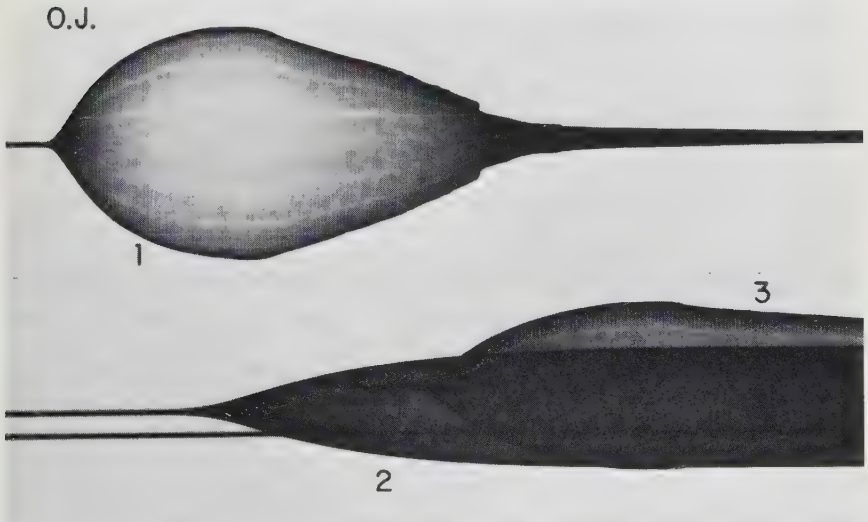

Figure 8. Mild lysis, corrected by heparin. *1*, Mild fibrinolysis; 2, partial heparinization; 3, after protamine.

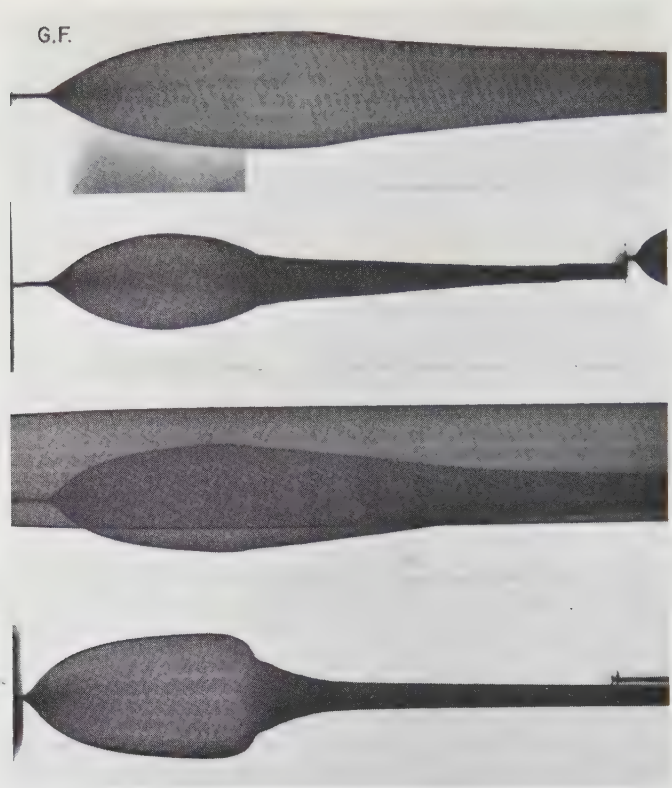

Figure 9. Consumption coagulopathy in septic shock. *Top*, Decreased platelets, with some lysis; *Second*, increased lysis, platelets still decreased; *Third*, effect of epsilon-aminocaproic acid; *Bottom*, return of lysis.

by $R = 11.5$) with more pronounced fibrinolysis (beginning at 13 minutes). The third tracing, taken in the recovery room, shows the cessation of both fibrinolysis and hypercoagulability. Confirmatory studies from the coagulation laboratory later demonstrated lytic breakdown products. This patient needed no therapy, as the surgical procedure was brief.

An example of milder fibrinolysis is seen in Figure 8. This pattern of lysis rarely causes significant clinical bleeding. The patient was undergoing aortic bifurcation graft when unusual oozing was noted. The second sample in Figure 8 reveals a severe plasma factor deficiency ($R = 52$), which in this patient indicated heparinization. What was believed to be 30 mg. of heparin (installed in the iliac arteries) turned out to be 150 mg., with subsequent partial heparinization of the patient. It would seem worth noting that this partially heparinizing dose (patient's body weight was 62.2 kg.) completely reversed the previously demonstrated fibrinolysis. The third tracing shows return of the clot toward normal after partial reversal of the heparin with 50 mg. of protamine (R now is 21).

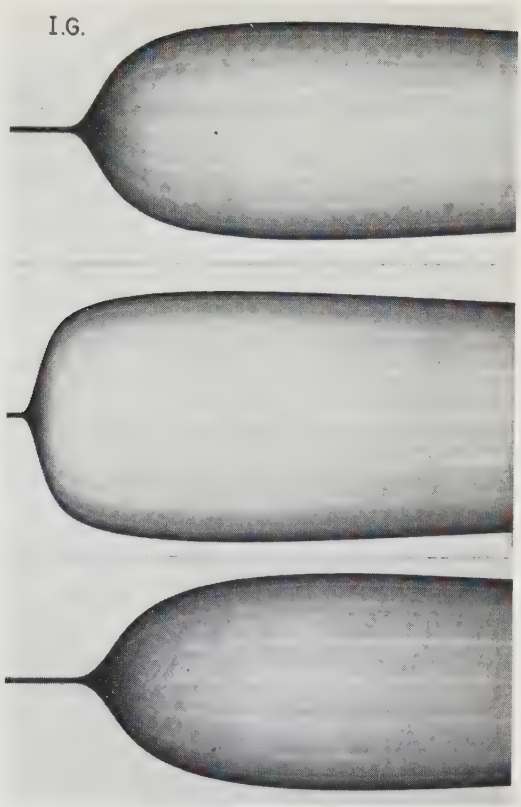

Figure 10. Liver disease. *Top*, After several days of vitamin K therapy; *Middle*, after fresh frozen plasma; *Bottom*, one day post operation.

A classic example of consumption coagulopathy is seen in Figure 9. This patient with Hodgkin's disease developed a mediastinal abscess which led to septicemia and shock. The first two tracings predominantly show decreased platelets (*AM* was 30 → 32 and platelet count at this time was 9000). After treatment with epsilon-aminocaproic acid, fresh frozen plasma, 5 per cent albumin suspension, whole blood, and platelet transfusions (as well as antibiotics, etc.), her clot showed no improvement in width on the following morning (consumption was still taking place – tracing 3, Fig. 9) and lysis began after 15 minutes. Institution of a slow drip of 5 gm. of EACA did result in improvement in the fibrinolysis, as seen in the fourth tracing of Figure 9. This is one illustration that shows that a slow, steady infusion of EACA is more effective against lysis than intermittent doses, presuming, of course, that the underlying cause of the fibrinolysis cannot be eradicated. Despite further vigorous therapy, including mannitol and vasodilators as well as the aforementioned therapies, the patient's condition deteriorated. The bottom tracing in Figure 9 shows the increased lysis and continuing narrow clot (*AM* = 40) which was present immediately preceding her death (which was apparently caused by massive tumor invasion of her mediastinum and lungs).

Figure 10 shows an unusual sequence of events. This patient had an exploratory laparotomy for metastatic disease to the liver (with concomitant abscess formation) from an unknown primary. Preoperative Vitamin K therapy had brought her prothrombin time to a normal level of 12.9 seconds (control 13). Platelet count was 362,000, glass clotting time 9'44", and fibrinogen level was 860 mg. per 100 ml. (this unusually high fibrinogen level was presumably a residual compensatory mechanism) (see first tracing, Fig. 10). Since rather pronounced oozing was encountered during laparotomy, 250 ml. of fresh frozen plasma was administered prophylactically (though the unusual bleeding may have been caused by previous radiotherapy). The fresh frozen plasma caused her clot to become distinctly hypercoagulable (*R* went from 26 to 12½ and *AM* rose from 58 to 66) (middle tracing, Fig. 10). Presumably the hypercoagulability was caused by a boost of her plasma levels with fresh frozen plasma while she still maintained her compensatorily elevated fibrinogen level. By the following afternoon, the clot had returned to its preoperative levels (*R* was 28).

CONCLUSION

The above cases, illustrative of nearly 200 patients whom we have followed using the thrombelastograph, demonstrate the ease with which major clotting disorders can be diagnosed and monitored in the operating and recovery rooms. Results can be obtained rapidly and repeatedly, without interpretation by specialized personnel in an emergency, and rational therapy (rather than shotgun therapy for "possible" unusual bleeding) instituted.

ACKNOWLEDGMENTS

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REFERENCES

1. Gans, H., and Krivit, W.: Problems in hemostasis during open-heart surgery. IV. On the changes in the blood clotting mechanism during cardiopulmonary bypass procedure. Ann. Surg., *155*:353-359, 1962.
2. Gans, H.: Thrombogenic properties of epsilon-aminocaproic acid. Ann. Surg., *163*:175-178, 1966.
3. Jean-Gilles, Brunet, Brockunier, Alfred and Ryan, Gail, M. Case Report, Consumption Coagulopathy Associated with Multiple Cavernous Hemangiomas. (in preparation)
4. Krevans, J. R., and Jackson, D. P.: Hemorrhagic disorder following massive whole blood transfusions. J.A.M.A., *159*:171, 1955.
5. Leeming, Michael, N. Ryan, Gail, M. and Howland, W. S.: Rapid Readout Device for Thrombelastography. J. Lab. Clin. Med. (in press).
6. Leroux, G. Marchal, et Samama, M.: Thrombelastography. Atlas de Thrombodynamographic. Service de Propagande, Paris 9e.
7. Naeye, Richard, L.: Thrombotic state after hemorrhagic diathesis, a possible complication of therapy with epsilon amino caproic acid. Blood, *19*:694, 1962.
8. Stefanini, M.: Studies on the hemostatic breakdown during massive replacement transfusion. Amer. J. Med. Sc., *244*:298, 1962.
9. Zucker, M. B., Siegel, M., Cliffton, E. E., Belville, J. W., Howland, W. S., and Grossi, C. E.: The effect of hepatic lobectomy on some blood clotting factors and on fibrinolysis. Ann. Surg., *146*:722-781, 1957.

Carcinoma of the Thyroid in Children

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During a 30-year period (1933–1962), 1214 patients with carcinoma of the thyroid were admitted to the Memorial Sloan-Kettering Center for Cancer and Allied Diseases. Of these, 62 were children below the age of 16. Although in our experience relatively few thyroid cancers are found in this age group, they make up a significant proportion of the malignant solid tumors of childhood.

There is evidence that the diagnosis of cancer of the thyroid is now made more frequently than in former years. Whether this represents an actual increase in the frequency of this disease is uncertain. Carroll[1] states that in New York state there has been a reported threefold increase in the incidence of cancer of the thyroid during the past 20 years, for patients under the age of 30 and an increase of 2½ times for patients aged 30 to 54. Patients 55 and over have the highest incidence of thyroid cancer, and this has not changed in recent years. Winship,[19] in his study of 562 cases of thyroid cancer in children gathered from the world literature, noted a marked increase in the incidence of this disease after 1945. In our series, three quarters of the cases were observed after 1945.

ETIOLOGY

Genetic

Genetic factors are inconclusive; there is no real evidence of a hereditary or familial tendency in this disease. There was thyroid disease in only two immediate families of the 62 children seen at Memorial Center. One patient's mother had a goiter, and one child's maternal grandmother had thyrotoxicosis; both lesions were benign.

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Sex

In this series 80 per cent of the girls dated the onset of their thyroid disorders after the age of 8 years. In the boys, 50 per cent of the tumors were diagnosed earlier, and the remainder were uniformly distributed throughout ages 9 to 15. The association of onset of disease and puberty in girls seemed evident, although menstrual histories were not well documented in all cases. One child had a lump in her neck for 2 years, but rapid growth of the tumor began after her first menstrual period.

Multinodular Goiter and Cancer

According to Russell,[15] there is no evidence that multinodular goiter is related to thyroid cancer in normal circumstances. Many years ago, Wegelin[18] observed an increase in thyroid cancer in regions of Europe where goiter was endemic, compared to other areas. Pendergrast,[10] in a more recent study, found no correlation between endemic goiter and thyroid cancer in this country.

Exposure to Ionizing Radiation

EXPERIMENTAL. Doniach[3] showed experimentally that thyroid cancer could be produced in rats exposed to ionizing radiation. He found that rats fed methyl thiouracil and radioactive iodine, or those given methyl thiouracil and external radiation, developed thyroid cancer. External radiation or radioiodine alone did not produce cancer, nor did MTU alone.

CLINICAL. In 1949 Quimby and Werner[13] were the first to suggest a possible association between radiation therapy of the thyroid gland for hyperthyroidism and the subsequent development of thyroid carcinoma. In 1950 Duffy and Fitzgerald[4] reported 28 cases of thyroid cancer in children seen at Memorial Center. They noted that nine of these children received short courses of low-voltage x-ray therapy for "enlarged thymus gland" during infancy. During the 1930–1940 period this treatment was popular, gradually falling into disfavor when it was realized that these were normal thymus glands, and that irradiation might cause serious thyroid pathology later in life.

A continuing study by Hempelmann and associates[8, 11, 12, 17] has followed 2878 persons who received thymic irradiation in infancy. The incidence of thyroid cancer in this group (0.7 per cent) is approximately 700 times that in the general population. One subgroup of 268 patients, who received a mean dose of 353 R, had a 30 per cent incidence of thyroid nodularity and a 4.3 per cent incidence of thyroid cancer. Winship[19] notes that 38 per cent of his patients had received previous irradiation to the thyroid region. Most had had radiation to the thymus in infancy, but there were many who had been treated for enlarged tonsils and adenoids, hemangiomas, nevi, acne, eczema, or cervival adenitis. Clark[2] reported 15 patients with childhood thyroid cancer, every one of whom gave a history of x-ray therapy in infancy for various benign conditions.

In the present series 13 gave a positive history of previous irradiation to the head and neck area, 10 to the thymus gland, one to the neck for

cervical adenitis, one to the adenoids, and one to the orbit for retinoblastoma. In all reported cases the dosages varied between 180 and 6000 R, with a mean of 600 R.[19] The interval between exposure to irradiation and the development of thyroid cancer varied from 3.6 to 14 years, with a mean interval of 8.7 years.

Radioactive Fallout. Fission of uranium-235 and plutonium-238 produces a high yield of iodine-131, which, with a half-life of 8 days, can be assimilated into the thyroid gland in large doses from delayed fallout. Since 30 per cent of the ingested ^{131}I is fixed in the thyroid gland for several weeks, it constitutes a grave radiation hazard.

The Bikini Accident. During the 1954 atomic tests, the fireball of a 15 megaton thermonuclear device touched the land and ocean, drawing up large amounts of radioactive dust, which settled on Rongelap Island, 100 miles downwind. There were 64 Marshall Islanders who received 175 rads total body irradiation; 19 were children, and 15 of them or 80 per cent later developed thyroid nodules or hypothyroidism. Three adults developed nodular goiter, one subsequently proving to be cancer. To date, however, none of the children have developed thyroid cancer.

Hiroshima and Nagasaki. Socolow et at.[16] have studied the survivors of the atomic bombing of these cities in 1945. Of 15,000 survivors studied, 21 developed thyroid cancer. This is a marked increase over the incidence in the general Japanese population, which is now 0.7 per 100,000. The bomb survivors developed thyroid cancer much earlier than is usual for this disease. Socolow's study showed that those survivors closer to the hypocenter, and those in the younger age groups, were more likely to develop thyroid abnormalities.

MEMORIAL CENTER SERIES

Of the 62 children reviewed, 43 were seen before any definitive treatment had been given, and these patients were regarded as having primary cases. This group included 21 patients who were seen before any type of surgery and 21 who were seen after biopsy of a neck node (18) or thyroid nodule (3). The remaining primary case was a child who died of generalized Ewing's sarcoma, in whom a small papillary thyroid carcinoma was found at autopsy.

The 19 secondary cases were in patients who had had definitive surgery elsewhere and came to Memorial Center for further surgical or medical treatment.

Age and Sex (Fig. 1)

The patients in this series ranged in age from 4 to 15 years. The youngest patient was a 4-year-old girl, whose neck mass had been noted 6 months previously. In Winship's series, the youngest patient was 4 months old, but he also describes 12 cases whose thyroid nodules were present at birth, and later proved to be thyroid cancer.

In this series 40 patients were girls and 22 were boys. This 2:1 ratio is similar to that in other reported series of childhood thyroid cancer, but somewhat less than the adult ratio, which is about 3:1.

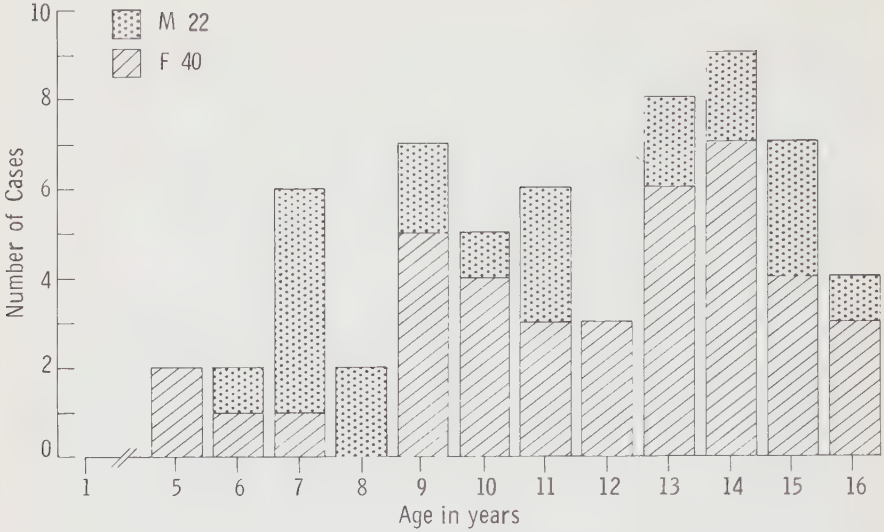

Figure 1. Age at diagnosis, 1933 to 1962.

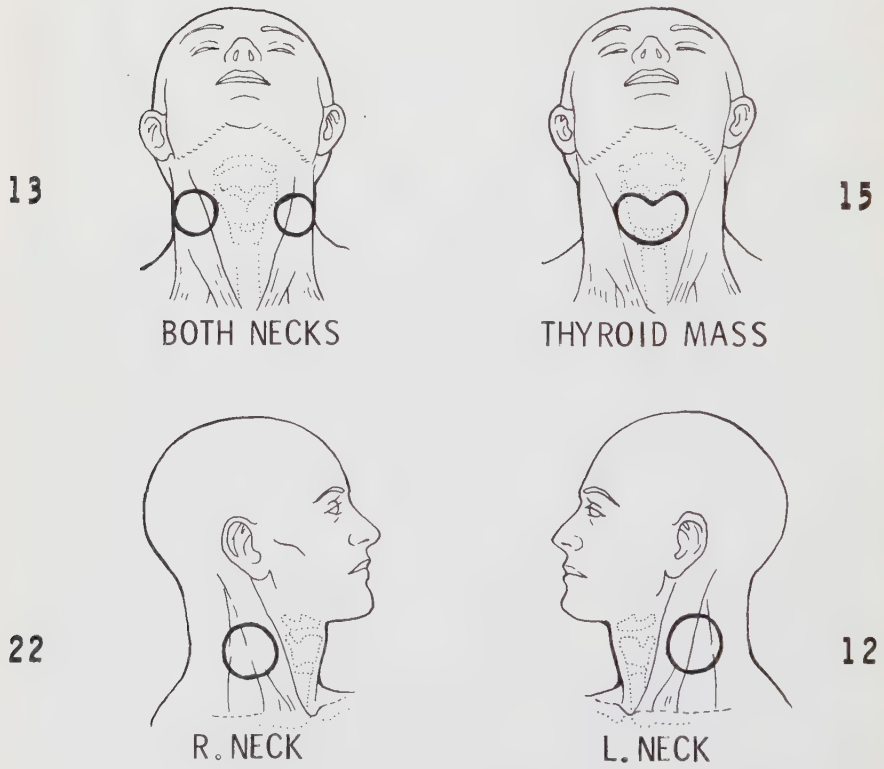

Figure 2. Initial presentation.

Admission Findings (Fig. 2)

Most of our patients presented with cervical lymph node metastases. A lump in the lateral neck was the initial complaint in 47 children (75 per cent); in the other 15 the complaint was of a mass in the anterior neck or thyroid region. Three children presented only when the enlarging tumor had begun to cause respiratory difficulty. Hoarseness was present in only one patient, and dysphagia in two others.

Most of the children had "lumps in the neck" for long periods. The average duration of symptoms prior to definitive diagnosis was 2 years. In one extreme case, where respiratory distress was the main complaint, a neck mass had been present for 9 years.

As noted, the main physical finding was palpable lymph nodes in the lateral neck. The nodes varied in size from 0.5 to 5 cm., the average being 2.5 cm. In many cases multiple nodes were present, and in 13 cases bilateral neck nodes were felt at the time of the initial presentation. Careful examination of the thyroid gland revealed the primary lesion in all cases. Usually a solitary nodule was felt in one thyroid lobe. The thyroid nodules varied in size between 2 and 5 cm., the average being 2.5 cm.

Two patients had recurrent laryngeal nerve paralysis due to involvement with carcinoma, both children having very advanced local disease. Seven patients had lung metastases present on chest x-ray at the time of the first visit to this hospital.

Laboratory Findings

Histology (Table 1). The great majority of our patients had low-grade forms of thyroid cancer, accounting for the favorable prognosis of this disease in children as compared to adults. The pathologic findings in the 62 cases in this series were comparable to those of Winship's series.[19]

Metastases. There were histologically proven metastases to cervical lymph nodes in 52 of the 62 cases (87 per cent). The involved lymph nodes were largely in the mid and lower jugular chains. This distribution of metastases is similar to that described by Frazell and Foote[6] in a review of papillary thyroid carcinoma in all age groups.

Lung metastases were seen at some stage in the disease in 13 patients (20.8 per cent). This did not necessarily imply a poor prognosis,

Table 1. *Laboratory Findings*

Papillary and follicular	25
Papillary	22
Papillary and alveolar	3
Alveolar and follicular	2
Papillary, follicular, and solid	2
Follicular and solid	2
Adenocarcinoma	2
Follicular	1
Papillary, follicular, and alveolar	1
Spindle cell (right lobe) and Hürthle cell (left lobe)	1
Solid, spindle, and giant cell	1

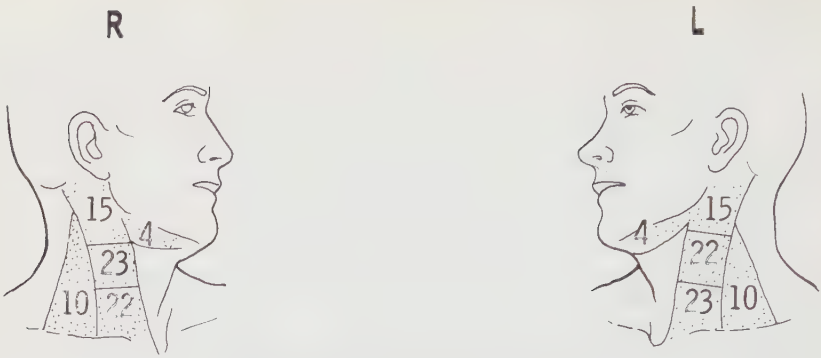

Figure 3. Proven metastases to neck (52 of 62 cases, or 87 per cent). Lung metastases occurred in 13 of 62 cases—20.9 per cent.

but the three patients who died showed uncontrolled disease at this site. Metastasis to the lung was not limited to one pathologic variant. Four of the 13 patients had papillary carcinoma, four had mixed papillary and follicular tumors, one papillary and alveolar, one solid carcinoma, and one spindle and giant cell. The tumor type in two cases was not specified. In one case, the primary thyroid tumor was papillary and alveolar cell carcinoma, while many years later, at the time of death, the lesion in the lungs was of the spindle and giant cell type.

Metaplasia to more anaplastic variants is well known in thyroid cancer, having been documented by Frazell and Foote[6] and by Hutter et al.[9]

There was only one case of bone metastasis in this series. In contrast, there is an incidence in adults of 6.5 per cent of bony metastases in papillary carcinoma, 4.5 per cent in follicular and alveolar, and 25 per cent in solid carcinoma. Winship[19] and Hayles[7] also report a low incidence of bone metastases in childhood thyroid cancer.

Treatment

SURGICAL. At Memorial Center, surgery has been the treatment of choice for thyroid cancer, both for the primary lesion and regional cervical lymph node metastases. The extent of surgery employed has been governed by the clinical presentation. Unilateral thyroid lobectomy is invariably carried out for lesions confined to one lobe. Resection of the lobe and the isthmus, plus subtotal resection of the second lobe, is performed for more extensive tumors or those involving the isthmus. Total thyroidectomy is rarely recommended because of the high incidence of postoperative parathyroid dysfunction.

In the presence of detectable cervical lymph node metastasis, or where previous lymph node biopsy showed metastatic disease, radical neck dissection is performed in continuity with the thyroid resection. Where both sides of the neck show lymph node involvement, staged bilateral radical neck dissection is performed.

In this series, 75 per cent of the children showed evidence of cervical lymph node metastasis as an admission finding, and in 87 per cent there was subsequent histologic proof of metastatic disease in the cervical

nodes. The high incidence of occult lymph node spread seemed to justify elective neck dissection, in the absence of clinically palpable neck nodes. Whether or not elective neck dissections contribute to long-term salvage in such patients has not been demonstrated. Currently, radical neck dissections are not done routinely in the absence of clinically involved nodes. These patients are followed carefully for a prolonged period, and if there is later evidence of cervical lymph node metastasis, radical neck dissection is performed at that time. The type of surgery carried out in this series is summarized in Table 2.

Biopsy. It has not been the policy to biopsy the thyroid gland or neck nodes at Memorial Center, but to proceed with elective surgery based on clinical findings and frozen section diagnosis at the time of the elective procedure. Where biopsies were performed on the patients in this series, it was done prior to their being seen at this hospital.

Radioactive Iodine. Radioiodine treatment was reserved for eight patients with metastasis to the lung and in whom tracer doses of radioiodine demonstrated pick-up in the lung lesions. Four patients treated with radioiodine had complete clearing of the lung lesions, while in the remaining four, lung metastases were controlled for varying periods of time. One child in this group developed radiation fibrosis of the lungs, which proved fatal 2 years later. Tracer doses of radioiodine are administered to all patients with lung metastases from thyroid cancer, regardless of the histologic type of tumor. Those showing pick-up in the lung metastases are then given iodine-131 in a dosage sufficient to eliminate any residual thyroid gland tissue. A second dose of radioiodine is then given (after a variable interval) and hopefully is picked up exclusively by the lung nodules.

External Irradiation. This mode of treatment is rarely employed in the treatment of thyroid cancer in this hospital. In most cases, an adequate surgical operation can control thyroid cancer in the neck; if it does not, external irradiation adds little to the control of the disease. Only one patient in this series received irradiation to the neck after thyroid lobectomy and radical neck dissection. Five with secondary cases received irradiation to cervical lymph nodes prior to coming to Memorial Center. One such patient received 7000 rads, through four portals, to the

Table 2. *Type of Surgery Performed*

Thyroid lobectomy	3
Thyroid lobectomy + subtotal resection of the contralateral lobe	2
Thyroid lobectomy + radical neck dissection	25
Thyroid lobectomy + subtotal resection contralateral lobe + radical neck dissection	5
Thyroid lobectomy + subtotal resection contralateral lobe + staged bilateral neck dissection	14
Total thyroidectomy + laryngectomy + staged bilateral radical neck dissection	2
Radical neck dissection	2
TOTAL	53
No surgery performed at Memorial	9

*Thyroid lobectomy elsewhere.

left side of the neck, and appeared to have permanent regression of the tumor. However, this child subsequently required thyroid lobectomy and dissection of the other side of the neck for persistent disease. He showed extensive neck scarring, as well as severe stunting of growth of the left neck and forequarter.

Two other patients had large doses of irradiation to both sides of the neck, and both of them subsequently required surgery for uncontrolled cancer on one side, although the opposite side of the neck showed no residual tumor. Two other patients who had received x-ray therapy for cervical lymph node metastases subsequently required radical neck dissection. It is apparent that control of the cancer was not achieved by external irradiation in any of these cases.

End Results

SURGICAL MORTALITY. There were 69 operative procedures carried out on the 62 patients in this series, with one death, a mortality rate of 1.5 per cent. The one death occurred in a patient who required thyroidectomy, laryngectomy, and staged bilateral neck dissection for advanced disease invading the trachea. On the third day after the second neck dissection, there was a "blow-out" of the innominate artery, and the child died of uncontrolled hemorrhage.

COMPLICATIONS. There were 20 complications of the surgery, most of which were related to sacrifice of various structures in an attempt to eradicate the cancer. Eight patients were left with varying degrees of hypoparathyroidism, some of whom required permanent replacement therapy. Nine had intentional sacrifice of one recurrent laryngeal nerve due to cancer spread. Children tolerated this complication well, and most made a full functional recovery in terms of voice and respiratory function. Two patients developed pneumothorax postoperatively, requiring tube thoracotomy, with complete recovery. Many patients were left with varying degrees of thyroid deficiency as a result of the radical nature of the surgery employed.

MORTALITY RATE. Of the 12 deaths in this series (Table 3), only three patients died of thyroid cancer and one of a postoperative complication. Of the eight who died of other causes, residual thyroid cancer was present in three at the time of death. Three patients were lost to follow-up. The mortality in 51 determinate cases was 7.8 per cent (Table 4).

SURVIVAL. There were 47 survivors who have been followed 5 years or more, representing a 5-year survival rate of 92.1 per cent. In this group eight are living and well 20 years after treatment. A total of 20 patients have survived 15 years or more, and 35 patients are living and well 10 years after initial treatment (Table 4).

SUMMARY

Sixty-two cases of thyroid cancer in children have been seen at Memorial Center between 1933 and 1962. Although this is an uncommon disease in children, it has been recognized with increasing frequency in recent years. The relationship between thyroid cancer and

Table 3. *Summary of Deaths*

PATIENT	SEX	AGE AT ONSET	PATHOLOGY	SURVIVAL TIME	CAUSE OF DEATH
W.B.	♂	16	Spindle and giant	9 months	Lung metastases
A.B.	♂	16	Papillary and alveolar	20 years	Lung metastases (spindle and giant)
L.S.	♂	9	Adenocarcinoma	6 years	Lung metastases
V.V.	♀	5	Follicular and solid	–	Innominate artery "blow-out" postoperatively
N.L.	♀	4	Papillary, follicular and solid	2 years	Respiratory obstruction after oophorectomy; thyroid Ca present in lungs
G.F.	♀	15	Papillary	13 years	Radiation fibrosis of lungs; thyroid cancer present in lungs at autopsy
L.K.	♀	10	Spindle and Hürthle	10 years	Sudden death, cause unknown
L.B.	♀	14	Papillary	3 years	Respiratory infection; autopsy showed no cancer
S.M.	♀	9	Papillary and follicular	7 years	Respiratory infection; autopsy showed no cancer
W.M.	♂	13	Papillary and alveolar	6 years	Rheumatic heart disease; lungs showed thyroid cancer at autopsy
C.D.	♀	13	Papillary and follicular	12 years	Malignant neurolemmoma, no evidence of residual thyroid cancer
J.R.	♀	15	Papillary	–	Ewing's sarcoma; papillary thyroid cancer was an incidental autopsy finding

Table 4. *End Results*

Total patients observed		62
Indeterminate results		
Lost to follow-up	3	
		11
Died of other causes	8	
Determinate results		51
Failures: Dead of disease or treatment	4	
Successes: Alive at last report	47 (92.1%)	
Alive 20 or more years	8	
15 or more years	20	
10 or more years	35	
5 or more years	47	

ionizing radiation in infancy is discussed, also the increased risk in children exposed to atomic radiation. In girls there is a strong suggestion that the onset of puberty may activate, or potentiate, thyroid cancer.

The delay between onset of symptoms and diagnosis is emphasized, accounting for the advanced stage of disease when many of these patients were seen at Memorial Center.

Surgery is the treatment of choice if the cancer is confined to the neck, and radioactive iodine is sometimes effective in controlling lung metastases.

The over-all prognosis in childhood thyroid cancer is good, provided that adequate surgery is performed. The morbidity and mortality of surgical treatment is low, and children recover rapidly from this type of surgery. A cure rate of 92.1 per cent was achieved in this series, and there is no doubt that this figure would be improved further by earlier diagnosis and treatment.

REFERENCES

1. Carroll, R. E., Haddon, W., Jr., Handy, V. H., and Wieben, E. E.: Thyroid cancer: Cohort analysis of increasing incidence in New York state, 1941-62. J. Nat. Cancer Inst., *33*: 277, 1964.
2. Clark, D. E.: Association of irradiation with cancer of the thyroid in children and adolescents. J.A.M.A., *159*:1007-1009, 1955.
3. Doniach, I.: Experimental induction of tumours of the thyroid by radiation. Brit. Med. Bull., *74*:181, 1958.
4. Duffy, B. J., and Fitzgerald, P. J.: Cancer of the thyroid in children; a report of 28 cases. J. Clin. Endocrinol., *10*:1296, 1950.
5. Frazell, E. L., and Foote, F. W., Jr.: Natural history of thyroid cancer. J. Clin. Endocrinol., *9*:1023-1030, 1949.
6. Frazell, E. L., and Foote, F. W., Jr.: Papillary cancer of the thyroid: A review of 25 years of experience. Cancer, *11*:895-922, 1958.
7. Hayles, A. B., Kennedy, R. L. J., and Beahrs, O. H.: Management of the child with thyroid cancer. J.A.M.A., *173*:21-28, 1960.
8. Hempelmann, L. H., Pifer, J. W., Burke, G. J., Terry, R., and Ames, W. R.: Neoplasms in persons treated with x-rays in infancy for thymic enlargement. J. Nat. Cancer Inst., *38*:317, 1967.
9. Hutter, R. V. P., Tollefsen, H. R., De Cosse, J. J., Foote, F. W., Jr., and Frazell, E. L.: Spindle and giant cell metaplasia in papillary carcinoma of the thyorid. Amer. J. Surg., *110*:660, 1965.
10. Pendergrast, W. J., Milmore, B. K., and Marcus, S. C.: Thyroid cancer and thyrotoxicosis in the United States: Their relation to endemic goiter. J. Chronic Dis., *13*:22, 1961.

11. Pifer, J. W., Toyooka, E. T., Murray, R. W., Ames, W. R., and Hempelmann, L. H.: Neoplasms in children treated with x-ray for thymic enlargement. I. J. Nat. Cancer Inst., *31*:1333, 1963.
12. Pincus, R. A., Reichlin, S., and Hempelmann, L. H.: Thyroid abnormalities after radiation exposure in infancy. Ann. Int. Med., *66*:1154, 1967.
13. Quimby, E. H., and Werner, S. C.: Late radiation effects in roentgen therapy for hyperthyroidism. J.A.M.A., *140*:1046, 1949.
14. Robins, J., Rall, J. E., and Conard, R. A.: Late effects of radioactive iodine in fallout. Ann. Int. Med., *66*:1214, 1967.
15. Russell, W. O., Clark, R. L., Ibanez, M. L., and White, E. C.: Intraglandular distribution of thyroid cancer as shown by whole organ subserial sections. Amer. J. Path., *34*:552, 1958.
16. Socolow, E. L., Hashizume, A., Neriishi, S., and Niitani, R.: Thyroid cancer in man after exposure to ionizing radiation. A summary of findings in Hiroshima and Nagasaki. New Eng. J. Med., *286*:406, 1963.
17. Toyooka, E. T., Pifer, J. W., Crump, S. L., Dutton, A. M., and Hempelmann, L. H.: Neoplasms in children treated with x-ray for thymic enlargement. II. J. Nat. Cancer Inst., *31*:1357, 1963.
18. Wegelin, C.: Malignant disease of the thyroid gland and its relation to goiter in man and animals. Cancer Rev., *3*:297, 1928.
19. Winship, T., and Rosvall, R. V.: Childhood thyroid carcinoma. Cancer, *14*:734, 1961.

Breast Lesions in Young Girls

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Pathological conditions which occur in the breast at the time of puberty or during adolescence are relatively uncommon and, with extremely rare exceptions, are of a benign nature. They do, however, present diagnostic and therapeutic problems, because it is during these years that the mammary glands may have developmental abnormalities due to premature or excessive growth of the breast tissue; these, as a rule, require no treatment.

In reviewing the records of the Breast Service at the Memorial Hospital from 1958 to 1968, a total of 237 girls with ages from 10 to 20 years at the time of hospitalization were found to have breast lesions for which some form of surgical treatment was given. It is estimated that this number represents almost 2 per cent of all the patients who were seen and treated by the service during this 10-year period.

All of the patients in this study had a histologic diagnosis. Therefore, those having abnormal developments which were clinically diagnosed as pubertal mastitis or virginal hypertrophy have been excluded.

DISTRIBUTION

Based on microscopic findings, 181 (76.4 per cent) of the patients had fibroadenomas, 25 (10.5 per cent) various forms of mastopathies, 13 (5.5 per cent) intraductal papillomatosis, 8 (3.4 per cent) gross cysts, 7 (2.9 per cent) inflammatory lesions, and 3 (1.3 per cent) malignant tumors. It should be pointed out, however, that in some instances it was difficult to make a clear-cut decision as to how to classify a lesion. For instance, a specimen may be listed as showing a combination of pathological conditions, such as papillomatosis and sclerosing adenosis, or fibrous mastopathy in the surrounding tissues may be added to fibroadenoma. Such cases were listed under what was considered the pre-

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Table 1. *Types of Breast Pathology in 237 Girls from 10 to 20 Years of Age.*

PATHOLOGY	No.	NO.	%
FIBROADENOMAS		181	76.4
a) adult type	169		
b) juvenile type	12		
MASTOPATHIES		25	10.5
a) fibrous	11		
b) periductal	5		
c) adenomatoid	4		
d) sclerosing adenosis	4		
e) lobular hyperplasia	1		
PAPILLOMATOSIS		13	5.5
GROSS CYSTS		8	3.4
INFLAMMATORY LESIONS		7	2.9
a) fat necrosis	5		
b) abscesses	2		
MALIGNANT TUMORS		3	1.3
a) primary carcinoma	1		
b) metastatic sarcoma	2		
TOTAL		237	100.0

dominant condition. A second problem was that bilateral lesions were sometimes of a different histologic type. Thus, a patient may have a fibroadenoma in one breast, while the lesion removed from the opposite breast is reported as fibrous mastopathy. In order to avoid duplication of numbers we have listed these patients in only one group. Although the number of cases presenting these problems is small, they do to a slight extent limit the complete accuracy of the frequency rates.

FIBROADENOMAS

Fibroadenomas are by far the most common pathological conditions which appear in the female breast between puberty and age 20. In this study 181 (76.4 per cent) of the patients were diagnosed as having such lesions. Of these, 169 (93.3 per cent) had tumors which were clinically and histologically similar to those seen in adults. There were 12 patients who had a variant of the adult type, and these have been designated as having juvenile fibroadenomas.

Among those having the adult type, 103 were white, 63 were Negroes, 2 Chinese, and 1 an American Indian. Their ages ranged from 12 through 19 years, with an average of 17.6 years. Age at menarche varied from 10 to 16 with an average of 12.4 years. All but 15 were recorded as having regular menses; 12 were married, and four of these were pregnant at the time of treatment.

Symptoms are relatively mild or entirely absent. Slight pain or tenderness may occur, but in most instances these slow-growing tumors are discovered by accident or during a routine examination.

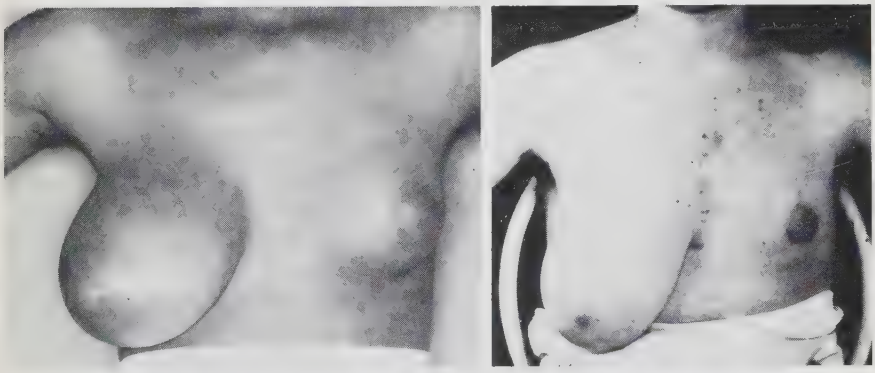
Clinical findings reveal a solid and firm lesion which is encapsulated and has a smooth or lobulated surface. It is freely movable and may occur in any part of the breast, but is usually eccentric to the areola. Those in this study ranged from 0.8 to 6 cm. in diameter, with an average of 2.5 cm. Thirty-nine patients (23 per cent) had multiple simultaneous lesions, of which 18 were unilateral and 21 bilateral. Multiplicity was more often seen in Negroes than in whites. Thirty-three patients developed additional fibroadenomas subsequent to the initial therapy.

Depending upon the size, location or multiplicity of the tumor, the treatment is by local excision through a radial, circumareolar, or peripheral curved incision. It should be noted that while these lesions are apparently encapsulated, the capsule is very thin and it is better to remove a small area of the surrounding stroma than to shell out the lesion.

Of the 12 patients having juvenile fibroadenomas, eight were Negroes and four were white. Their ages varied from 10 to 18, with a median of 14 years. Two patients had not begun to menstruate, while in the others the age at menarche varied from 10 to 14 years. Three were recorded as having irregular menses.

The usual complaint was a rapid and painless enlargement of the breast. The duraton prior to treatment ranged from 3 weeks to 4 years, with an average of 10 months. Most of the delay was due to the difficulty in differentiating clinically between juvenile fibroadenoma and unilateral virginal hypertrophy (Fig. 1).

Juvenile fibroadenomas are usually solitary, quite large, slightly firm, and round or oval, with a smooth surface. They are freely movable and encapsulated, but their consistency is sometimes so similar to that of the surrounding breast tissue that a clear-cut demarcation is not always easy. In this study they varied in size from 2.5 to 19 cm. In a few in-



Juvenile Fibroadenoma

Virginal Hypertrophy

Figure 1. Comparison of juvenile fibroadenoma (age 13) and unilateral virginal hypertrophy (age 11).

stances more than half of the breast was involved. Although the overlying skin may be tense, it does not adhere to the tumor. As the size of the lesion increases, the breasts become asymmetrical, which is one of the observations that distinguishes juvenile fibroadenoma from unilateral virginal hypertrophy. Another distinguishing finding is the prominence and dilation of the superficial veins above the tumor. Although the areola may be stretched out and appear enlarged, the nipple may be undeveloped.

Another condition which may be confused clinically with juvenile fibroadenoma is cystosarcoma phylloides, which in our experience is very uncommon in teenagers. Only two cases have been listed in our records, and both of these occurred several years prior to the time covered by this study.

Juvenile fibroadenomas may be bilateral, but only two patients in this group had bilateral lesions. Regardless of the size, one should, of course, avoid a simple mastectomy. When the lesion is quite large, it can be removed easily through a type of incision first suggested by Gaillard Thomas in 1882. This is a curved incision at the lateral or inferior border of the breast.

MASTOPATHIES

Included in this category are those diseases which are generally considered as being partly of a chronic inflammatory nature and, in some instances, with changes consistent with benign new growths. Of the 25 patients in this group, 11 were diagnosed histologically as having fibrous mastopathy, five periductal mastitis (nonsuppurative), four fibroadenomatoid mastopathy, four sclerosing adenosis, and one lobular hyperplasia. Although there were microscopic differences, the clinical findings were similar.

The ages of these patients at diagnosis varied from 13 through 19 years, with an average of 16.8. The onset of menstruation had occurred between 9 to 16 years of age, with an average of 12.5 years. Eighteen were listed as having regular menses and seven as having irregular periods, with the interval varying from 20 days to 3 months. Seven were listed as white and eight were Negroes; six of the latter had only fibrous mastopathy. Six patients had bilateral lesions, five of them similar and one a fibroadenoma.

Symptoms were absent or relatively mild. There were varying degrees of tenderness, which was frequently accentuated during the immediate premenstrual period. The physical findings varied, but in general the lesions were persistent, had grown slowly, and were described as localized, fairly well defined, firm, and freely movable. The size of the localized lesions varied from 1 to 4.5 cm., and six were described as totally or partly underlying the areola, while 18 were away from the central part of the breast. One patient had extensive and diffuse involvement of both breasts.

Because of their location, most of these lesions were removed through small radial incisions.

Figure 2. Bilateral fibroadenomatosis in a patient only 13 years old.

Included in this group was one very unusual case (Fig. 2). This patient, aged 13, had noted a persistent and rapid enlargement of both breasts about one year prior to her menarche, which occurred at 12½ years. After the onset of menses, her periods were irregular, but the enlargement of her breasts continued. At the time of bilateral mammoplasties, the circumference of the left breast was 61 cm. and of the right 59. The superficial veins were very prominent, but there was no tenderness or discrete nodules. Endocrine studies revealed no abnormalities. The surgical specimens were reported as unusual and slightly resembling the cell changes seen in male gynecomastia. The final diagnosis was fibroadenomatosis.

INTRADUCTAL PAPILLOMATOSIS

Of the 13 patients in this group, 12 were white and one was a Negro. They were between 15 and 19 years old, the average being 17.3 years. The menarche was listed as occurring from ages 10 to 17, with an average of 12.9 years. The menses were regular in nine and irregular in four.

There were relatively few symptoms. Nine patients had accidentally or because of slight tenderness noted an abnormal thickening or enlargement of the breast. Three reported a spontaneous bloody nipple discharge, but in one of these the discharge came from an accessory duct opening about halfway between the nipple and the areolar margin. Also, one of the patients having a bloody discharge from the right nipple gave a history of an operation in another hospital 3 years previously for a

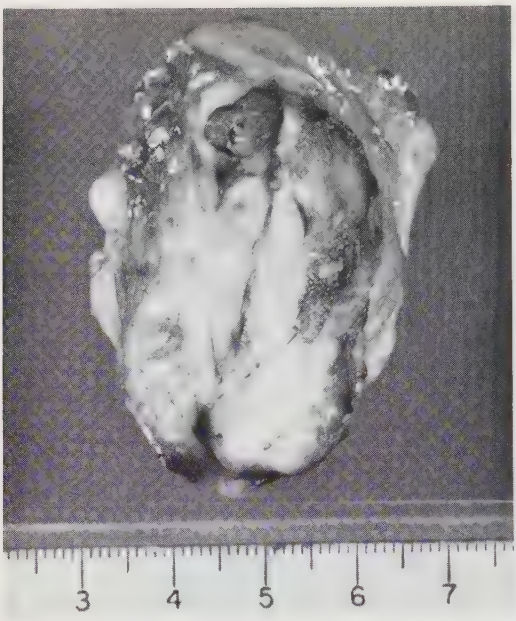


Figure 3. Intraductal papilloma from a girl 16 years of age.

bloody discharge from the left nipple. At the time of her first operation she was 15 years of age.

The physical findings varied considerably; two patients were described as having slight thickening of a major duct, while all the others were reported as having well-defined nodules or thickenings. Three such thickenings were described as being in the periphery of the breast tissues.

Most of the lesions were removed through circumareolar incisions without disturbing the entire major duct system.

There were two unusual cases in this group. The first was in a patient, aged 16, with a cluster of confluent and discrete nodules in the upper and outer quadrant of the left breast. When these were removed through a circumareolar incision, they were reported as showing extremely atypical papillomatosis. Frequent follow-up examinations were advised, but no recurrences or new lesion have been detected during the past 2 years.

The second was a Negro, aged 16, who, with one exception was normally developed and having irregular menses which began at age 12. The unusual finding was an excessive growth of hair on her face, chest, arms, and legs. Endocrine studies failed to reveal any specific abnormalities. For 3 months she had been aware of a bloody and, later, lemon-yellow discharge from the right nipple. The excised specimen showed a well-defined, pedunculated intraductal papilloma (Fig. 3).

GROSS CYSTS

There were eight patients in this group and, in contrast to the usual multiplicity of these lesions in adults, all but one had only a solitary

cyst. Their ages ranged from 12 through 17 years, with an average of 14.6. One patient, aged 12, had had no menses, while the average age at which the menarche had occurred in the others was 13.4 years. Five were having regular periods, while two were having irregular menses.

There were very few symptoms. One patient complained of tenderness, one had noticed a slight greenish nipple discharge, and three had observed a small, localized bluish discoloration of the skin near the inner margin of the areola.

The physical findings were fairly uniform in that a majority of the lesions were described as being well circumscribed, small (about 1 cm. in diameter), and freely movable. Most were located within or adjacent to the areolar margin. Although in three patients the cysts were reported as showing chronic inflammation, the fluid contents were usually clear and gave no evidence of an infection.

These lesions were removed through circumareolar incisions.

INFLAMMATORY LESIONS

Under this heading there were five patients who had localized fat necrosis and two who had abscesses. Ages ranged from 14 through 19, with an average of 16.6 years. The age at menarche averaged 13 years, and three were noted to have irregular menses.

Among the patients listed as having fat necrosis, all but one had noticed localized tenderness, but none gave a history of injury. One had noticed a whitish, thick nipple discharge, while another gave a history of having a fibroadenoma removed from the breast about a year previously.

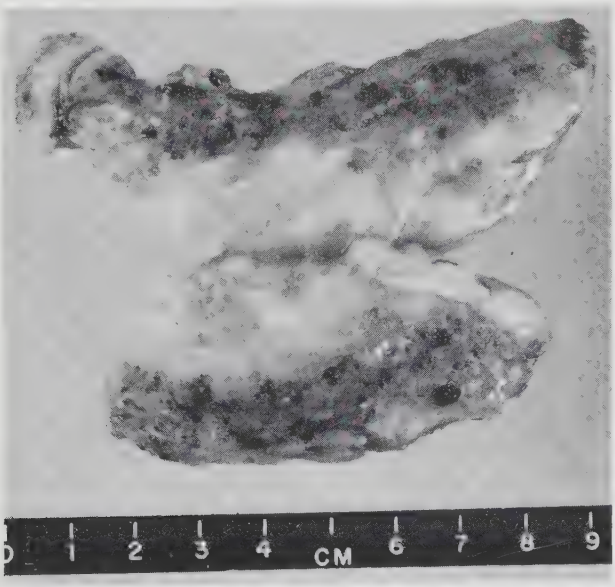


Figure 4. Combination of localized sclerosing adenosis, cysts and duct stasis in a girl 16 years old.

Her specimen was described as showing fat necrosis with a foreign body reaction. All of the lesions were located within or near the areolar margins and were usually described as tender, well-defined nodules. Usually they were excised through circumareolar incisions.

Of the two patients having abscesses, one, aged 17, had a large abscess in the outer and lower quadrant of the left breast. She had experienced pain for about 2 weeks with acute tenderness and localized redness of the overlying skin. Incision was performed and about 50 ml. of thick pus was removed. With drainage and antibiotics, the lesion healed without complications. The second patient had a recurrent inflammatory lesion a year after having a periductal abscess incised and drained. The excised specimen contained multiple, very minute abscesses.

MALIGNANT TUMORS

There was one patient who had a primary breast cancer. Among the many thousands of women with breast cancer who have been seen by the Breast Service at the Memorial Hospital, she is the youngest and only the second under 20 years of age listed as having mammary carcinoma. The first patient, within a few months of her nineteenth birthday, was treated in 1951 by a radical mastectomy for a highly malignant lesion. Although there were no identifiable secondary deposits in the axillary lymph nodes, widespread and rapidly fatal metastases appeared within 2 years.

The present case is to be published in detail later. Briefly, the patient was 17½ years of age and gave a history of having a bloody discharge from the right nipple shortly after her first period, when she was 12½ years old. Following this she had amenorrhea for 6 months and then was given small doses of contraceptive pills at irregular intervals for about 3½ years. Six months after these were stopped and shortly after her seventeenth birthday, she noticed bilateral breast nodules at the margin of the areolae. When these were excised, the specimen from the right breast was reported as being of a juvenile type of breast cancer which has been described in detail by McDivitt and Stewart.[1] The lesion from the left breast was reported as showing intraductal papillomatosis and sclerosing adenosis. Subsequently, when a right modified radical mastectomy was performed, the axillary lymph nodes were free of metastases. Although follow-up examinations have been limited to 9 months, there has been no evidence of recurrent disease, and the patient is healthy and very active.

Two patients had metastatic sarcomas within the breast tissue. Both were 14 years of age and also had secondary deposits in other areas from primary embryonal rhabdomyosarcomas that had originated in the facial muscles. Clinically the lesions were nontender, discrete, hard, and freely movable. One patient had two lesions in the left breast, while the other, a Negro, had multiple bilateral metastases. The sizes varied from 1 to 5.4 cm., and none was located in the central part of the breast. Both patients were being treated by chemotherapy, but there was limited

objective response; in fact, the metastases in the breast slowly increased in size and additional areas appeared prior to death.

CONCLUSION

The distribution of pathologic lesions occurring at the time of puberty or during adolescence in 237 girls has been presented. As expected, a considerable majority had fibroadenomas similar to those seen in adults. The percentage having multiplicity of these lesions, both simultaneously and consecutively, was more than double that which has been observed in adults.

Although the majority of the lesions in this study occurred in white girls, there seemed to be a rather significant racial relationship in two groups. Eight of the 12 having juvenile fibroadenomas were Negroes, while 12 of the 13 having intraductal papillomatosis were white.

There seemed to be little relationship between the type of lesion and menarche or regularity of menses. The exception was that juvenile fibroadenomas as a group appeared at an early age and just before or within a short time after the menarche. In fact, fibroadenomas of an adult type as well as other benign lesions increased in numbers as sexual and breast maturation progressed.

Finally, it should be stressed with great emphasis that surgery should be avoided in young girls having unilateral prepubertal or postpubertal mastitis. This condition is by far the most common of those seen at the time of puberty or in early adolescence. It is characterized by a slightly tender, flat, round, finely nodular, and fairly well-defined thickening which symmetrically underlies the nipple and areola. In contrast, pathologic lesions are mainly eccentric to the areola. Even when occurring in the central part of the breast, they are localized and extend to or beyond the areolar margin in an irregular and asymmetrical manner.

REFERENCE

1. McDivitt, R. W., and Stewart, F. W.: Breast carcinoma in children. J.A.M.A., *195*:388-390 (Jan. 31), 1966.

Preoperative Radiation and Radical Neck Dissection

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Renewed interest in combined radiation and surgical treatment of cancer has been recently apparent. An exhaustive review of the history and current clinical experience with such combined therapy has recently been published.[1] Our dissatisfaction with the results of radical neck dissection for the local control of metastatic epidermoid cancer primary in the head and neck area led us, with the cooperation and assistance of the Department of Radiation Therapy, to the institution of a controlled prospective study of the effect of low-dose preoperative radiation to the neck, hoping to effect a reduction in the incidence of subsequent cervical recurrence. Preliminary reports of this study have been published.[2-4] The study has now been completed, and this communication presents the final results describing the total experience of the years 1960 to 1966 inclusive, with follow-up to July 1, 1968.

Details of the clinical protocol are outlined in Table 1. All ward patients who were candidates for radical neck dissection for epidermoid carcinoma of the head and neck were considered. Those patients who died postoperatively (19 controls, 11 radiated, and 2 others), or who died of any cause, including cancer, free of recurrence in the dissected neck within 12 months of surgery, were excluded. No second (contralateral) neck dissections have been included. Patients found to have unresectable tumor in the neck at surgery have also been excluded. Thus it is apparent why less than half of the neck dissections done by the Head and Neck Service during this period have been eligible for the study.

No attempt has been consciously made to pick or otherwise to match patients except as dictated by the protocol. If all eligible patients are to be included in such a clinical study it is obvious that the control and radiated series are not and cannot be exactly comparable as regards anatomic location of the primary cancer or extent of clinical disease. Four hundred twenty patients have been followed for a minimum of 12 and a maximum of 102 months. Certain candidates for preoperative

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Table 1. *Preoperative Radiation Protocol*

Ward or service patients only
Primary head and neck squamous or epidermoid cancer
No prior surgery or radiation to neck
No gross residual cancer left after radical neck dissection
No interstitial or postoperative radiation to neck
Minimum 12 months follow-up if free of cancer in the neck
Odd birthday – preoperative radiation
Even birthday – no preoperative radiation (control)

Table 2. *Distribution of Patients by Sex*

SEX	CONTROL	RADIATED	OTHER
Male	166 81.4%	120 83.3%	51 70.8%
Female	38 18.6%	24 16.7%	21 29.2%
Total	204	144	72

Table 3. *Distribution of Patients by Age in Decades*

	CONTROL		RADIATED		OTHER	
10 to 19	1		0		0	
20 to 29	1		1		0	
30 to 39	7		1		1	
40 to 49	21		14		6	
50 to 59	68	63.7%	55	68.1%	22	65.3%
60 to 69	62		43		25	
70 to 79	40		28		17	
80 to 89	4		2		1	
Total	204		144		72	
Average age	59.8 years		60.3 years		62.5 years	

Table 4. *Distribution of Cases in Time*

	CONTROL	RADIATED	OTHER	TOTAL
1960	26	30	6	62
1961	36	24	21	81
1962	44	18	16	78
1963	28	17	7	52
1964	30	22	8	60
1965	16	15	12	43
1966	24	18	2	44
	204	144	72	420

Table 5. *Distribution of Cases by Primary Site*

	CONTROL		RADIATED		OTHER	
Skin	3	1.5%	0	0.0%	1	1.4%
Lip	3	1.5	2	1.4	6	8.4
Buccal mucosa	14	6.9	5	3.4	1	1.4
Gum	15	7.3	11	7.7	6	8.3
Floor of mouth	31	15.2	26	18.3	10	13.9
Tongue	56	27.4	33	22.9	23	31.9
Palate	15	7.3	9	6.9	3	4.2
Tonsil	14	6.9	14	9.7	5	6.9
Nasal cavity	3	1.5	0	0.0	1	1.4
Paranasal sinus	1	0.5	1	0.7	3	4.2
Nasopharynx	3	1.5	5	3.4	2	2.8
Pharyngeal wall	6	2.9	7	4.8	0	0.0
Extrinsic larynx	28	13.7	25	17.4	10	13.9
Intrinsic larynx	12	5.9	6	4.1	1	1.4
	204	100.0%	144	100.0%	72	100.0%

radiation were in error not so treated, largely due to failure in communication. For completeness' sake these patients are listed separately as "others" and, as anticipated, they behaved clinically similar to the controls.

The patients are described in Tables 2 to 6. They do not differ from any other group of patients suffering from head and neck cancer. The incidence of histologically positive cervical lymph node metastases, one of the most important determinants of prognosis in head and neck (and other) cancer, is somewhat higher in the radiated than in the control series. Composition of the three groups is similar.

Irradiation was delivered to the entire neck from clavicle to mandible, chin to mastoid, via a single direct lateral port, in five equal treatments of 400 R on successive treatment days. The Allis-Chalmers betatron generating an electron beam of 18 MeV maximum energy was employed during the first 2½ years of the study. For practical reasons this has been supplanted by the ^{60}cobalt teletherapy unit, whose biological effects on the cervical tissues are similar. Indicated surgery was carried out as soon as possible upon completion of the radiation. Only

Table 6. *Status of Cervical Lymph Nodes*

	CONTROL			RADIATED			OTHER		
Clinical									
negative	83	40.7%		35	24.3%		25	34.7%	
positive single level	89	43.6	59.3%	89	61.8	75.7%	37	51.4	65.3%
positive multiple levels	32	15.7		20	13.9		10	13.9	
Pathological									
negative	75	36.8%		40	27.8%		21	29.2%	
positive single level	63	30.9	63.2%	50	34.7	72.2%	23	31.9	70.8%
positive multiple levels	66	32.3		54	37.5		28	38.9	

Table 7. *Miscellaneous*

	CONTROL	RADIATED	OTHER
Surgery done			
neck dissection only	22 10.7%	15 10.4%	16 22.2%
combined resection*	182 89.3%	129 89.6%	56 77.8%
Necks dissected			
right	110	76	43
left	94	68	29
(as part of simultaneous or staged bilateral)	29 14.2%	16 11.1%	4 5.5%
Average units of blood given during surgery	3.20 units	2.84 units	2.72 units
Average postoperative hospital stay	24.8 days	26.2 days	21.2 days

*Radical neck dissection combined with resection of primary lesion with or without partial mandibulectomy.

two patients are known to have any significant postradiation symptoms, and both demonstrated markedly heightened mucosal and skin reactions during their radiation.

No significant differences among the three groups with regard to surgery done, volume of blood replacement required during surgery, duration of postoperative hospitalization, or incidence of complications have been noted. Details of these aspects are enumerated in Tables 7 and 8.

Eighty-four per cent of all cervical recurrences occurred within the first 12 months postoperatively, 92 per cent within the first 18 months and 94 per cent within the first 24 months. Of the six cervical recurrences noted after 2 years, four were accompanied by prior or simultaneous recurrence at the primary site.

Table 8. *Complications*

	CONTROL	RADIATED	OTHER
Patients having one or more complications	70 34.3%	65 45.2%	24 33.4%
Carotid rupture	1	3	0
Fistulas			
closed spontaneously in hospital	13	4	7
open upon discharge or required secondary closure	15 = 28 = 13.7%	15 = 19 = 13.2%	5 = 12 = 16.7%
Chyle fistula	4	3	1
Wound slough requiring secondary closure	3	3	0

Table 9. *Results*

	CONTROL		RADIATED		OTHER	
Total number of patients	204		144		72	
Histologically positive nodes	129	63.2%	104	72.7%	51	70.8%
Recurrence at primary site	50	24.5	25	17.4	14	19.5
Recurrence in neck	75	36.8	34	23.6	25	34.7
Recurrence in neck with negative nodes	5/75	6.7	0/40	0.0	0/21	0.0
Recurrence in neck with positive nodes	70/129	54.3	34/104	33.4	25/51	49.1
Recurrence in neck with nodes positive one level	23/63	36.5	14/50	28.0	6/23	26.1
Recurrence in neck with nodes positive multiple levels	47/66	71.3	20/54	37.1	19/28	67.9
Minimal survival rate 3 years	49.7%		46.7%		53.9%	

The results of the study are outlined in Table 9. Fewer local recurrences at the primary site have occurred in the radiated patients, but the difference is not statistically significant ($p > 0.10$). The extent of disease has not been staged. It is impossible to calculate the amount of radiation delivered to each primary, except possibly in those patients whose primary cancers of the larynx, base of tongue, or pharyngeal wall were situated at or near the center of the radiation port. Combining radiation and subsequent radical neck dissection has significantly lowered the incidence of cervical recurrence ($0.01 < p < 0.05$), especially in those patients with advanced metastatic cancer involving cervical lymph nodes at more than one level, who are the patients with the poorest over-all prognosis.

Excluding the influence of local recurrence at the primary site upon the subsequent cervical recurrence by excluding all patients with this ominous combination does not significantly alter the differences in cervical recurrence rates—28.7 per cent in the controls vs. 17.6 per cent in the radiated patients. Five "control," one "radiated," and four "other" patients have been lost to follow-up 12 to 70 months postoperatively, all but one free of cervical recurrence. Were these nine patients considered to have recurrence for statistical purposes, the difference in recurrence rates between control and radiated series would be even greater. Although a significant reduction in the rate of cervical recurrence has been obtained by combined radiation and surgery, a concurrent prolongation of survival has not been produced. The patients have fared better in the dissected neck, but have often gone on to die of uncontrolled disease elsewhere.

SUMMARY

Low-dose radiation to the neck, followed promptly by radical neck dissection for epidermoid carcinoma of the head and neck area, has produced a significant reduction in the subsequent cervical recurrence rate without increasing morbidity or mortality. This local improvement

has not produced any significant increase in survival rate, however. We do believe that low-dose preoperative radiation is of value and now employ it routinely in suitable cases. A logical further step would appear to be combined radiation and surgery for both the primary cancer and its regional metastases.

The author acknowledges the advice and assistance of David Schottenfeld, M.D., in the statistical analyses.

REFERENCES

1. Cady, B.: Preoperative radiation. Surg. Gynec., Obstet., *126*:851-865, 1091-1105, 1968.
2. Henschke, U. K.: Frazell, E. L., Hilaris, B. S., et al.: Local recurrences after radical neck dissection with and without preoperative x-ray therapy. Radiology, *82*:331-332, 1964.
3. Henschke, U. K., Frazell, E. L., Hilaris, B. S., et al.: Value of preoperative x-ray therapy as an adjunct to radical neck dissection. Radiology, *86*:450-453, 1966.
4. Strong, E. W., Henschke, U. K., Nickson, J. J., et al.: Preoperative x-ray therapy as an adjunct to radical neck dissection. Cancer, *19*:1509-1516, 1966.

Bilateral Neck Dissection

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The presence or absence of metastasis to the regional lymph nodes is a matter of profound significance and probably affects the possibility of cure of cancer more than any other single factor. The anatomy of the lymphatic system of the head and neck is such that metastatic cancer may be isolated in lymph nodes in the region for long periods of time, giving the surgeon the opportunity to eradicate the disease by block dissection. Unilateral neck dissection has been successfully employed in this clinic and elsewhere for many years. Experience taught that a complete ipsilateral neck dissection was to be preferred to a partial neck dissection. All too frequently healing of a supra-omohyoid or some modified form of neck dissection was obtained, only to find a node just beneath the operative area, requiring re-entry and dissection in a scarred field with less chance of control than if a complete dissection had been done initially. It was also learned that the standard neck dissection could be performed bilaterally in stages without undue risk to the patient. Since 1950 simultaneous dissection of both sides of the neck, often combined with resection of the primary cancer, has been practiced by the Head and Neck Service of Memorial Hospital. During this period 234 simultaneous bilateral neck dissections have been carried out.

ANATOMY AND PHYSIOLOGY

The lymphatic system of the head and neck is orderly and rich. The terminal lymph vessels collect the lymph in the capillary system, passing their collections to larger afferent channels leading to lymph nodes. After filtration through the node the lymph passes into the efferent vessels, toward the right lymphatic duct and the thoracic duct in the left neck, and on into the subclavian vein. Cross connections between the lymph nodes, both on the same side and on the opposite sides of the neck, may be rich. It is possible for metastatic disease to skip the proximal lymph nodes entirely and be seen first in a lower node than one would expect, or even occasionally in contralateral neck nodes.

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*Assistant Attending Surgeon

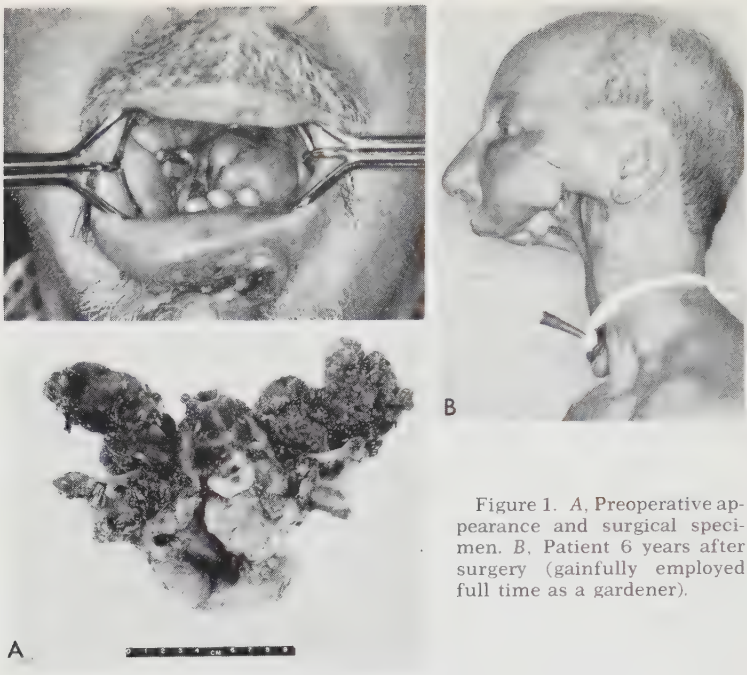

Figure 1. *A*, Preoperative appearance and surgical specimen. *B*, Patient 6 years after surgery (gainfully employed full time as a gardener).

Venous Drainage

The richness of the venous drainage of the head and neck makes possible the eradication of important venous plexuses while leaving adequate venous routes to properly drain the cranial cavity, the face, and the neck. In addition to the internal and external jugular veins, and in order of importance, the veins are as follows: (1) the external and internal vertebral plexuses with their communicating veins (the major pathway after ligation of the jugulars); (2) the occipital vein; (3) the posterior jugular vein; (4) the deep cervical vein; (5) collecting veins of the posterior cervical region; and (6) the pharyngo-esophageal and pterygoid plexuses. The venous systems are related by an extensive communication system connecting the intracranial and extracranial portions of the head via emissary veins, with the flow mainly toward the extracranial areas; these allow reduction of venous congestion of the brain when the jugular circulation has been blocked. The total cross-sectional area of the vertebral venous system has been estimated to probably exceed that of the jugular veins. Occasionally a patient who has undergone bilateral neck dissection has persistent marked cyanosis and edema of the face, but there is normal cerebrospinal fluid pressure and no evidence of increased intracranial pressure.

Cerebrospinal Fluid Circulation

Cerebrospinal fluid pressures during the course of bilateral neck dissection, as well as after the operation, have been studied in our clinic. The most marked rise in CSF pressure was noted to follow marked

flexion or turning of the head, when the pressure actually was higher than that noted when the internal jugular vein was ligated. When the head is returned to the midline position, pressures return to their previous levels. Increased intracranial pressures may also be markedly aided by keeping the patient in a reverse Trendelenburg position. According to Weed and O'Connell, there is a shift of cerebrospinal fluid to the lumbar region, resulting in a partial collapse of the cranial portion of the system, thus permitting increased intracranial venous distention without a marked rise of pressure. Occasionally permanent increase has been reported, even after unilateral neck dissection.

INDICATIONS FOR SURGERY

Bilateral cervical metastasis is obviously the chief indication for bilateral neck dissection. Occasionally massive direct extension into both sides of the neck is found, making staging impossible without cutting through cancer and also serving as an indication for bilateral dissection. Most of the patients in this series (more than 90 per cent) had primary cancers which were located in the midline and were, in order of occurrence, in the floor of the mouth, the larynx, and the tongue. Most of the lesions in the larynx were of the supraglottic or extrinsic variety, while most of the tongue lesions occurred in the base. The thyroid gland, lips, and gum were other midline structures involved. The clinical evaluation of the neck when the question of bilateral simultaneous dissection is at stake has been extremely accurate. The decision whether to perform bilateral neck dissection is an important one, as such an operation naturally carries an inherent risk of higher mortality and a higher complication rate. It has been our experience that the examiner may be very accurate in predicting the presence or absence of neck nodes under these conditions. Usually, of course, the cancer is so far advanced in these patients that the appreciation of the presence of metastasis is not difficult. The age of the patient should not be a factor in determining the indication for the operation. In our own series the youngest patient has been 15 and the oldest 83.

TECHNIQUE

In most instances the operation will be carried out in combination with excision of the primary tumor. The supine patient is positioned on the table with four folded sheets beneath the shoulders and two beneath the head. The neck is extended and the table so arranged that the patient is in a reverse Trendelenburg position. It is possible for two teams to work simultaneously during most of the operation, thus decreasing operating time. The chin is kept in the midline and the head turned only when necessary, such as when the internal jugular vein is ligated at its upper level. Upon completion of the neck dissection usually one team drops out, so that a single team carries out the excision of the primary tumor, wherever it may be located.

The surgical incision, as practiced by members of the Head and Neck Service at Memorial Hospital, has become more or less standard-

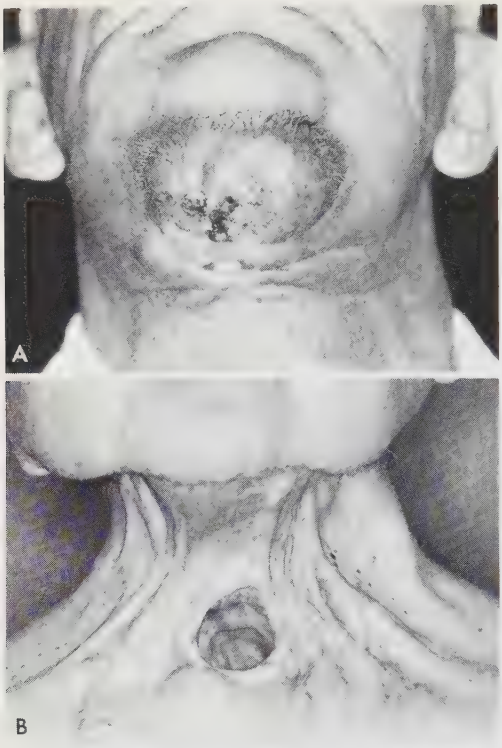

Figure 2. *A*, Preoperative appearance, showing recurrence following radiation therapy. *B*, Postoperative appearance 5 years after surgery. Note lack of edema but dilated vessels seen on skin surface.

ized, though it varies occasionally when indicated. It is begun at the mastoid process, brought downward and forward to the tip of the hyoid bone, and then dropped vertically downward to about 4 cm. above the midpoint of the clavicle, from which point it is angled outward and downward to reach the clavicle. This incision is made on both sides of the neck and the two incisions are connected by a horizontal incision made in the skin line at the level of the hyoid. When it is necessary to resect the central portions of the mandible, lip, or tongue, a block of tissue is excised so that the midportion of the lip and the skin lying beneath it is sacrificed if necessary to produce a good closure. The skin flaps are raised and a complete dissection is carried out upon each side.

It is to be emphasized that when simultaneous bilateral neck dissection is done a complete operation upon both sides is meant. The internal jugular veins, the sternocleidomastoid muscles, and the contents of the neck, to include as much of the lymphatic system as possible, are removed. Blood loss is monitored by weighing sponges and blood replacement in accordance is carried out. Usually the blood is passed through a blood warmer to avoid rapid transfusion of large amounts of cold blood. The operation is completed by the insertion of a tracheostomy tube, which is left in place until all danger of postoperative edema has passed. Suction drainage tubes are placed on either side of the neck and a very light, nonobstructive dressing is applied. It is best to keep the patient's head and neck elevated.

Often at the completion of the operation or in the immediate postoperative period the patient's face appears to be suffused and purplish. This is not cyanosis, but is due to venous congestion which occurs to a varying extent in all patients. Usually this has corrected itself at the end of the first 24 hours. Early ambulation is encouraged. Usually the edema due to the blockage produced by removal of the lymphatics begins on the third or fourth day and reaches its peak in 7 to 10 days. Persistent facial edema occurs in about 15 per cent of patients, and during its most marked period may be complicated by chemosis. No serious permanent complications have resulted.

OPERATIVE COMPLICATIONS

Operative complications are unfortunately a frequent sequel of an operation of this magnitude. The most frequent complication noted in our own series is an oropharyngeal fistula. Many of these occurred in patients who have been subjected to heavy previous radiation. Most such fistulas will close spontaneously, though occasionally secondary closure and plastic reconstructive procedures are necessary. The fistula per se is not dangerous, but the accompanying wound sepsis may be, leading in turn to skin and soft tissue necrosis and to possible rupture of the carotid

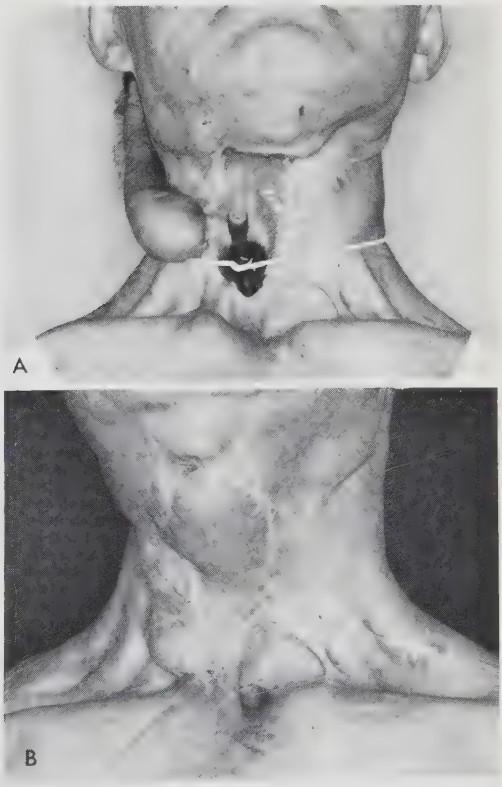

Figure 3. *A*, Postoperative appearance following bilateral neck dissection and laryngopharyngectomy. Reconstruction started. *B*, Reconstruction using migrated tube pedicles completed so that patient may eat in a normal fashion.

artery. Occasionally one may avoid this complication by the deliberate construction of a pharyngostoma rather than attempting primary closure, even though it seems technically possible.

The second most likely postoperative complication is loss of skin flaps. Usually, however, excess skin is present and necrosis of some of the skin flap is not a cause for serious alarm. However, when major loss occurs, exposing carotid arteries, danger of rupture arises. When oropharyngeal fistula or skin slough is thought likely (particularly in those patients who have had radiation), the artery and the mucosal suture line may be protected by the use of rotated muscle flaps, particularly the levator scapulae muscle.

When the patient has had a stormy anesthesia with marked coughing and straining, pneumothorax, usually bilateral, has occurred. Lately this complication has been rare, due primarily to the improvement in anesthesia. During the postoperative period the most common and probably one of the more serious complications has been aspiration of saliva with resultant pneumonitis. This can be the cause of postoperative death. The chronic degenerative diseases found in patients of the "cancer age" may be expected and dealt with as indicated.

POSTOPERATIVE CARE

After bilateral neck dissection, the immediate postoperative care is little different from that following any major head and neck procedure. The maintenance of an adequate airway with proper ventilation deserves the most critical attention. The airway should be kept sucked free of mucus. The proper positioning of the tracheostomy tube, well-humidified air, and supplementary oxygen as required, are points deserving of the attention of the recovery room attendants. The lightest of dressings are to be used, so as not to constrict the venous return. The patient's neck should not be kept upon a pillow, which might cut off venous return. Close watch on the proper function of the suction catheters should be maintained, so that hematoma may be avoided. The patient is kept in a semi-sitting position and, as a matter of fact, is most comfortable in this position. As soon as possible following reaction from the anesthesia the patient is put upon enteral feedings, via nasogastric or pharyngogastric tubes. Clear fluids are best in the beginning, rapidly increased to a full feeding formula as soon as possible. Early ambulation and bedside sitting is encouraged. The patient's intraoral wounds and tracheostomy tube are usually dressed twice daily. Pain is seldom a problem, and often one of the gratifying, immediate results following bilateral radical neck dissection is the relief from pain. All patients are routinely given antibiotics.

Expected Results

At the beginning of this article the serious prognostic significance of neck node metastasis was mentioned. All of our patients who required operations of this magnitude were patients with advanced cancer. However one may expect long-term survival in about 15 per cent of these patients. Productive and comfortable life has been extended in most

instances. The operative mortality will depend somewhat on the type of patient, but also on the experience of the surgeons involved in the operation and after-care. It should not be prohibitive, however, and the expected results may make the risk acceptable. Certainly the alternative left for the patient who is otherwise hopeless should encourage the surgeon.

Interim Prosthetic Management of Pharyngostoma and Esophagostoma

GEORGE P. ARGERAKIS, D.D.S.*

JAMES B. LEPLEY, D.D.S.**

The surgical treatment of bulky tumors of the head and neck may result in the creation of elective pharyngeal and esophageal fistulas. Primary closure of surgical defects may be complicated by lack of approximating tissues, poor blood supply, and previous irradiation. Any of these events may lead the surgeon to create a fistula at a suitable location where future complications would be kept at a minimum.

While the need for an elective tube feeding esophagostomy to aid difficult feeding problems is recognized, the stomas usually close spontaneously with no difficulty once the tube is removed. Large esophagostomas are usually the sequelae of radical surgical excision of exceedingly bulky tumors.

Prosthetic closure of a pharyngostoma or esophagostoma provides great assistance to the patient. The patient with a pharyngostoma cannot talk, swallow saliva, or take nourishment by mouth. The patient with an esophagostoma also cannot swallow or take nourishment by mouth. Such a patient may have had a laryngectomy and will not recover the ability to speak.

If these defects are closed with a prosthesis, the surgeon has greater control over the patient's diet, can evaluate the problem of aspiration, and can proceed with reconstructive surgical procedures in an orderly, planned manner.

During this prolonged wait, the patient may lead a more normal life with nearly restored physiologic function of speech and deglutition. This is a great boost to his morale.

Case 1.

A 77-year-old woman was admitted in December 1967 with a diagnosis of recurrent epidermoid carcinoma of the left buccal mucosa. She

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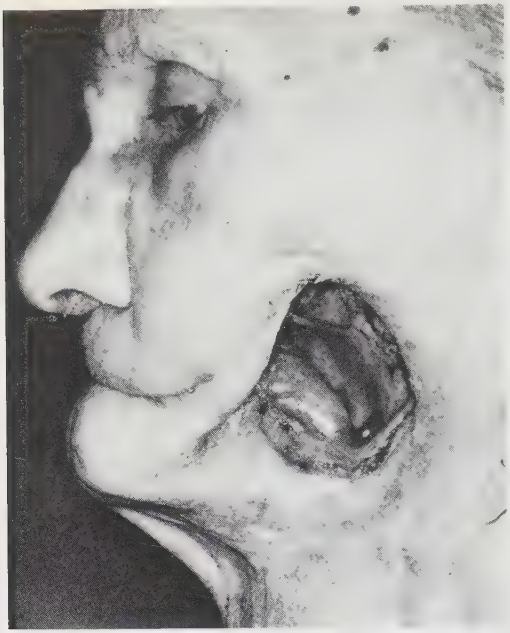

Figure 1 (Case 1). The defect resulting from surgical excision of the left buccal mucosa.

Figure 2 (Case 1). Silicone rubber prosthesis in position.

Figure 3 (Case 2). Pharyngostoma resulting from radical surgery for epidermoid carcinoma of the base of the tongue.

had had chemotherapy, irradiation, and surgical treatment for the disease, which had resulted in a hemimandibulectomy and the tongue had been sutured to the buccal mucosa. At this admission, wide excision of the left buccal mucosa resulted in a large defect lateral and posterior to the tongue (Fig. 1).

An alginate impression was made of the defect and adjacent external tissues, and a room temperature vulcanizing silicone rubber prosthesis

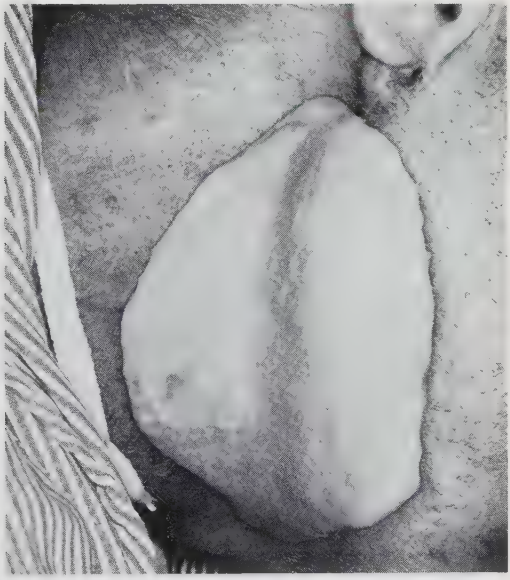

Figure 4 (Case 2). The prosthesis in place.

Figure 5 (Case 2). A modified Barton bandage used to retain the prosthesis.

was constructed (Fig. 2). The prosthesis functioned well, and the patient was able to talk, eat, and swallow. Unfortunately, she developed unmanageable recurrence of disease and was placed in a rest home in terminal condition.

Case 2.

A 53-year-old man was admitted in August 1967 with a diagnosis of epidermoid carcinoma of the base of the tongue. Right radical neck dissection, right subtotal mandibulectomy, resection of three fourths of the tongue, and pharyngectomy with construction of a pharyngostoma were done (Fig. 3).

An alginate impression was made of the defect and surrounding tissue. A silicone rubber prosthesis was constructed to close the pharyngostoma (Fig. 4). With the prosthesis retained in place by use of a modified Barton bandage, the patient was able to talk and swallow saliva and a soft diet without aspirating (Fig. 5). Pressure of swallowing and constant moisture precluded the use of adhesive, a situation that existed in all three cases described. Evaluation eliminated the need for laryngectomy, and the patient retained his larynx. He was able to return to work while awaiting reconstructive surgical efforts.

Case 3.

A 60-year-old woman was admitted in September 1967 with the diagnosis of epidermoid carcinoma of the larynx and cervical esophagus.

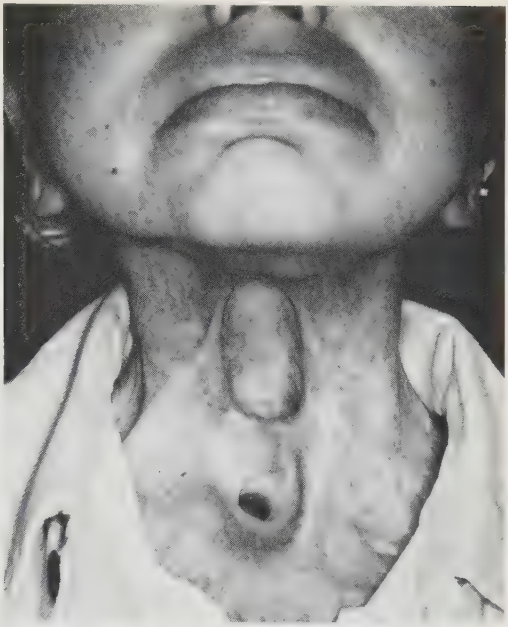

Figure 6 (Case 3). An esophagostoma.

Her history included radiation therapy for thyroid cancer 20 years before. She underwent total laryngectomy and cervical esophagectomy. A subsequent surgical effort to close the defect by means of a pectoral tube graft failed (Fig. 6).

An alginate impression of the defect and adjacent areas was made.

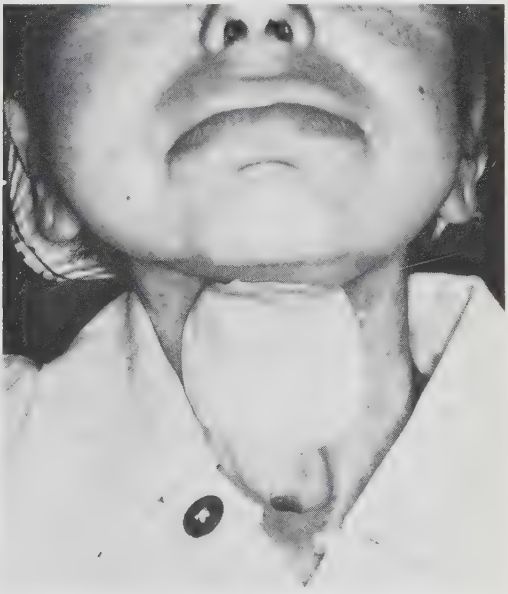

Figure 7 (Case 3). The prosthesis in position.

A prosthesis was formed from silicone rubber, which successfully closed the defect and enabled the patient to eat a soft diet by mouth for the first time in 9 months (Fig. 7). The prosthesis was held in place by means of an elastic bandage.

Summary

Elective formation of esophagostomas and pharyngostomas is often an essential part of staged surgery for removal of bulky tumors of the head and neck. Three cases of interim prosthetic management of these defects have been described.

Biopsy of the "Normal" Breast in Treating Breast Cancer

JEROME A. URBAN, M.D.*

The "normal" breast which does not present any apparent physical signs of breast cancer not infrequently contains this lesion in its noninfiltrating in situ stage, or, less often, as an occult infiltrating cancer. Since current curative treatments of breast cancer represent local attacks on the primary tumor and its regional nodal metastases, which succeed only when the tumor is localized, and since systemic therapy is unpredictable and temporary at best, detection and treatment of breast cancer while it is still in its early stage of development represents the greatest challenge and offers the most promise for improvement in the control of this disease. Routine detection of breast cancer usually depends upon the so-called "classic signs"—palpable mass in the breast, skin attachment and dimpling, nipple retraction, presence of firm and enlarged axillary nodes, etc.—all of which represent late signs of breast cancer. Such detection represents no tremendous achievement, since lesions which present these signs are already of long duration and many unfortunately have already established occult distant metastases which will eventually negate any curative attempt.

"Hard core" statisticians have only recently conceded that there has been some improvement in the salvage of patients with breast cancer in the United States. This improvement has been frustratingly slow and of small degree. Although some credit should be given to improved methods of primary therapy—particularly the use of supervoltage x-ray therapy and, in some instances, application of more complete surgical procedures—it is likely that most of the improvement has been due to earlier detection and treatment of more localized lesions. The prognosis in breast cancer is directly proportional to the extent of disease present.

DIAGNOSTIC APPROACHES

Several methods for early diagnosis have been utilized during the last few decades. (1) Self-examination has been promoted primarily by

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the American Cancer Society[4] and has resulted in many patients detecting early palpable lesions of their breasts. These patients often seek medical advice with minimal lesions. It is impressive that more than 90 per cent of breast cancers are still found by the patient. (2) Cancer Detection Clinics[6] uniformly have reported a high proportion of Stage I cancers of the breast detected by careful examination of asymptomatic patients attending these centers. In most instances axillary nodal involvement falls below 30 per cent incidence, and the 5-year salvage rate, with routine treatment, exceeds 90 per cent. (3) Cytologic examination of nipple secretion by and large has been disappointing since most breast cancers cannot be detected in this manner.

(4) Many early localized cancers of the breast have been detected through a liberal policy of excising minimal lesions of the breast for pathologic examination, even though the usual clinical signs of breast cancer were not present. Most lesions detected in this manner are relatively localized in extent. In 1960[11] we reported on such a program and demonstrated that 11 per cent of local excisions performed for clinically benign or indefinite breast lesions revealed carcinoma. The incidence of axillary node involvement in this group was half that found in patients undergoing surgery at the same time for carcinomas which were clinically apparent. The 5-year salvage rate with conventional therapy was more than 70 per cent in patients with occult breast cancers and only 50 per cent in those treated for clinically apparent lesions. This policy of excising persistent, doubtful, or clinically benign lesions of the breast is generally accepted, has resulted in the detection of a significant number of early cancers, and undoubtedly has contributed to improved control of this disease. Occult breast cancers have been detected in a similar proportion of patients undergoing excision of the major duct system for apparently benign intraductile lesions producing nipple discharge.[12] Examination of the surgical specimen in 150 patients undergoing excision of the major duct system revealed 11 with either noninfiltrating intraductal carcinoma or in situ lobular carcinoma. Four showed minimal infiltrating lesions and only one of the latter had a positive axillary node. All of these patients are free of disease following definitive therapy.

(5) X-ray mammography and thermography have been utilized in the first nationally organized attempt to detect minimal early lesions of the breast on a large scale. Impressive findings have been reported by many roentgenologists. X-ray mammography when done with excellent technique and interpreted with painstaking care not only has revealed some occult infiltrating cancers but also, in some instances, has demonstrated the presence of noninfiltrating in situ lesions, both of the intraductal and lobular type. These findings represent solid achievements in this field. However, like most diagnostic methods, mammography has its limitations and is only about 70 per cent accurate in most situations. Mammography should be utilized to demonstrate the need for excisional biopsy before this need is apparent on physical examination. It is not a substitute for biopsy. A negative mammogram in the presence of a suspected lesion should be disregarded and an adequate biopsy taken.

Undue reliance upon a negative mammogram at times has proved disastrous for the patient. A negative mammogram simply indicates the absence of any suspicious x-ray signs in the breast; it does not rule out the presence of carcinoma in the breast.

Between 1961 and 1967, 3000 of our own patients were examined by x-ray mammography. In most instances these were patients with equivocal findings or who had symptoms without any physical findings in the breast. They comprise a difficult group of patients and very rarely included patients with clear-cut breast cancer. In this group of 3000 patients we were influenced to operate on 28 in whom x-ray mammograms revealed suspicious findings despite the lack of clinical signs. Fourteen of these patients proved to have carcinoma of the breast; nine had noninfiltrating in situ lesions and five had infiltrating cancers. All of these carcinomas were at an early stage of development. This represents a real achievement for x-ray mammography. On the other hand, during the same interval, we operated upon 28 other patients in whom carcinoma was suspected even though x-ray mammograms showed no suspicious sign of cancer. In this group we found 21 infiltrating cancers and 7 noninfiltrating in situ cancers—demonstrating the lack of reliability of a negative mammogram for ruling out the presence of breast cancer. Despite its limitations, the record of mammography in the field of early diagnosis of breast cancer has been impressive. Further improvements in technique and interpretation will undoubtedly occur and will add to the accuracy and practicality of this diagnostic method.

(6) The most promising field for detection of early breast cancer is the contralateral breast of a patient successfully treated for proven cancer in one breast. In 1945, Foote and Stewart[3] said, "The most frequent antecedent of cancer on one breast is the history of having had cancer in the opposite breast." Bloodgood[1] in 1921 and Pack[9] in 1951 advocated prophylactic simple mastectomy of the opposite breast at the time of mastectomy for a proven breast cancer. Leis[7] in New York City performed a series of prophylactic simple mastectomies in a selected group of patients who had been treated for a primary breast cancer, who were given a good prognosis, and who were suspected of having a high risk of developing contralateral cancer. In this series of 66 patients, seven unsuspected cancers were found in the opposite breast. Hubbard[5] and Farrow[2] were more conservative in their approach and advised that prophylactic simple mastectomy be performed only under special circumstances—after a suitable disease-free interval following primary therapy, with a strong family history of breast cancer, or when significant atypia was noted in the second breast on biopsy.

Robbins and Berg[10] in 1964 showed that almost 1 per cent of patients who have undergone mastectomy for proven breast cancer will develop a new breast cancer in the opposite breast each year following treatment. They also stated that the over-all risk for development of a new primary in the opposite breast in these patients was five times greater than that in the general female population. Newman[8] in 1963 showed a particularly high incidence of bilaterality for in situ lobular carcinoma of the breast: more than 23 per cent of his patients. The reported inci-

dence of simultaneous bilateral primary breast cancer varies from 0.1 to 2 per cent, and the incidence of asynchronous bilateral breast cancer varies between 1 and 12 per cent, depending upon the authors, the patients studied, and the duration of follow-up. It is likely that as an increasing number of patients with good prognoses are treated adequately, the incidence of new primary lesions in the opposite breast will increase along with prolonged survival.

We have become increasingly aware of the bilaterality of breast cancer as well as of the difficulty of detecting this lesion during its early stages of development. We have seen patients previously successfully treated for primary cancer in one breast return beyond hope of salvage with an advanced inoperable cancer in the opposite breast following a long delay in follow-up examination. We have detected a number of unsuspected breast cancers by generous biopsy of minimal clinical findings. Generous controlled surgical biopsy has detected cancer in one half of our own patients who had suspicious x-ray mammograms, but who were free of any detectable physical signs. In reviewing the 10-year survival rates for extended radical mastectomy some years ago, we were impressed to find that 9 per cent of the original patients undergoing this procedure had developed a new primary in the opposite breast in the interim. This combination of factors has influenced us to biopsy the opposite breast with increasing frequency. During the last 2 years we have adopted this as a routine procedure.[14]

CASE REPORT

Case report demonstrating the difficulty of detecting an occult primary cancer in the opposite breast. Patient S.S., the 36-year-old wife of a physician, was referred to us from Central America in March 1958 having had a 2 cm. infiltrating duct carcinoma excised from the upper outer portion of her left breast a week previously. The patient was asymptomatic and demonstrated a well-healed biopsy wound in the upper outer portion of the left breast with minimal underlying induration. A rubbery 1.5 cm. diameter node of questionable significance was noted in the lower portion of the left axilla. The neck was clear. A firm 2.5 cm. diameter node was noted in the right axilla and some minimal, diffuse, fibrous thickening was present in the tail of the right breast. We were uncertain whether we were dealing with bilateral primary breast cancers or possibly a metastatic lesion in the right axilla secondary to the primary tumor in the left breast. The skeletal survey, chest x-rays, and blood chemistries were reported within normal limits. Careful physical examination failed to reveal any other evidence of disease.

It was decided that this patient would be considered to have simultaneous bilateral breast cancer, provided that carcinoma could be found in the right axilla. Accordingly, at the time of surgery, aspiration biopsy of the node in the right axilla was performed and revealed metastatic cancer consistent with a breast primary. The patient then underwent a simultaneous bilateral radical mastectomy. She did well postoperatively. The final pathological examination revealed no residual tumor in the left breast, and all left axillary nodes were clear. The right breast contained a tiny primary breast cancer—an 8 mm. infiltrating duct carcinoma, Grade III—in its tail. Metastatic nodes were present at level I only (lower third) of the right axilla; the upper two thirds of the axilla was clear. The patient recuperated uneventfully and received prophylactic orthovoltage x-ray therapy covering the base of the neck and internal mammary chain on the right side through anterior as well as posterior ports, each port receiving 3000 R (in air) over a period of 4 weeks. This patient who still menstruates regularly is now asymptomatic and free of disease 10½ years postoperatively.

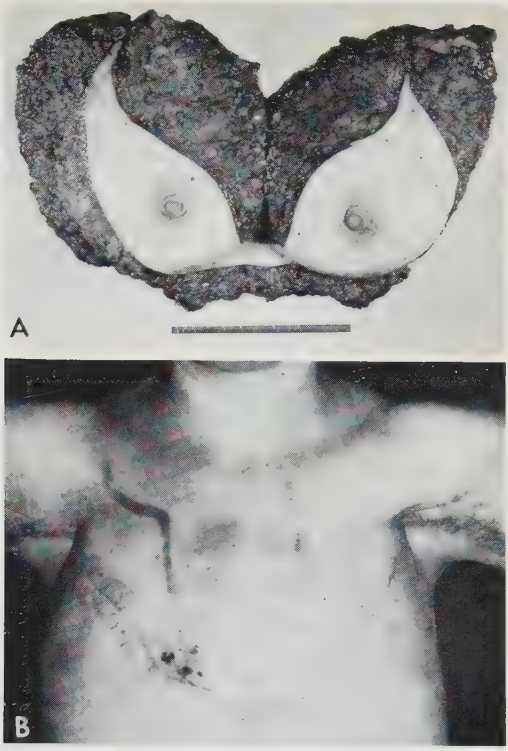

Figure 1.

CONTRALATERAL BIOPSY AND FINDINGS

Since January 1964 we have biopsied the opposite breast in 70 per cent of our own patients undergoing mastectomy for a proven breast cancer. Contralateral biopsy has not been done in patients with uncertain survival—mainly patients over 70 years of age and those with advanced lesions and a poor prognosis. The opposite breast was not available for biopsy in 5 per cent of patients, who had previously undergone mastectomy. Generous biopsy is most often done for minimal physical findings, and occasionally on the basis of a suspicious mammogram. When no physical or x-ray signs are present, a generous random biopsy is performed, including approximately 20 per cent of the breast parenchyma in the upper outer quadrant of the breast, where 60 per cent of breast cancers arise, plus the mirror image of the known lesion in the dominant breast, since approximately 40 per cent of bilateral breast cancers are symmetrical in location.

Table 1, based upon our own patients treated between January 1964 and August 1968, illustrates the relative yield of contralateral biopsies performed on the basis of minimal physical signs as compared with those done as a random procedure. Approximately 20 per cent of those done on the basis of minimal physical signs were positive, while 10 per cent of those done on the random basis revealed carcinoma, the over-all detec-

Table 1. *Results of Biopsy of the Contralateral Breast (422 Private Cases)*

Biopsies	Ca		Benign
	Infilt.	Non-infilt.	
95 random	2	7	86
186 min. sign	14 *	20	152
281 total	16	27	238
	15%		(11% atypical)

* 5 suspected preop

tion rate being 15 per cent of the contralateral breasts biopsied. (Five bilateral lesions included in this data were suspected clinically.) Some 11 per cent of benign biopsies were considered to be atypical—lobular hyperplasia or papillomatosis. The potential of these lesions for subsequent development of breast cancer is uncertain, but is probably at a significant level. Although we do not feel that we have sufficient grounds for performing prophylactic simple mastectomy on these patients, they are being followed closely with careful physical examinations every 3 or 4 months, and x-ray mammograms every 1 to 1½ years. They are biopsied generously at the first appearance of minimal physical signs. Several of these patients have already developed in situ cancers, as well as one infiltrating cancer, during a short follow-up period. Close follow-up of these patients with atypical lesions may yield worthwhile information regarding the development of breast cancer.

Table 2 evaluates the incidence of bilaterality for infiltrating and noninfiltrating breast cancer. The highest level of bilaterality is found in patients treated for in situ lobular carcinoma. In this group 30 per cent

Table 2. *Incidence of Bilateral Breast Cancer (422 Private Cases)*

Primary lesion and treatment	Number biopsied	Benign	Ca		Previous mastect.
			Infilt.	Non-infilt.	
366 infilt. ca (rad. or ext. rad.)	242	211	15*	16	15
56 non-infilt. (mod. rad.)	39	27	1	11	5
422 total	281 (70%)	238	16	27	20
			15% bilat. ca (10% simultaneous)		

* (5 suspected clinically)

Table 3. *Incidence of Bilateral Breast Cancer (289 Clinic Cases)*

Primary lesion and treatment	Number biopsied	Benign	Ca		Previous mastect.
			Infilt.	Non-infilt.	
259 infilt. ca (RM and MRM)	88	77	4	7	23
30 non-infilt. (RM and MRM)	18	11	2	5	7
289 total	106 (40%)	88	6	12	30
			16.6% bilat. ca (6% simultaneous)		

(17/56) were bilateral—5 had previously undergone mastectomy and 12 of 39 biopsied breasts revealed simultaneous carcinoma, one infiltrating and 11 noninfiltrating. Approximately 13 per cent (46/366) with infiltrating cancer were bilateral—15 had undergone mastectomy previously, and 242 simultaneous contralateral biopsies revealed 31 cancers in the opposite breast—16 noninfiltrating and 15 infiltrating. In the over-all group 70 per cent (281/402) of the available opposite breasts were biopsied. Sixteen infiltrating cancers and 27 noninfiltrating cancers were detected by such biopsies, while 20 patients had undergone mastectomy previously on the opposite side. This breaks down to a 15 per cent rate of bilaterality, 5 per cent asynchronous and 10 per cent simultaneous. All patients with simultaneous bilateral cancers were treated by simultaneous bilateral mastectomies—applying various combinations of the

Table 4. *Stage of Second Primary Breast Cancer (All Cases)*

	Infilt. ca	Nodes +	Non-infilt. ca
422 private cases			
43 simultaneous biopsy →	16	1 (6%)	27 (63%)
20 previous mastect.	19	6 (31%)	1 (5%)
↓ 20 current mastect.	15	4 (27%)	5 (25%)
289 clinic cases			
18 simultaneous biopsy →	6	2 (33%)	12 (66%)
30 previous mastect.	28	12 (43%)	2 (7%)
↓ 30 current mastect.	24	12 (50%)	6 (20%)

extended, classical, or modified mastectomy depending upon the clinical pathologic setting in each breast.[13]

Between October 1965 and August 1968, 289 clinic patients were treated for breast cancer (Table 3). In this group 40 per cent (106/259) of the opposite breasts were biopsied. Again, the highest rate of simultaneous bilateral cancer was found in patients treated for in situ lobular carcinoma, 40 per cent (7/18) of contralateral biopsies being positive. More than 10 per cent of these patients had undergone mastectomy previously for cancer in the opposite breast, while 6 per cent had simultaneous bilateral breast cancers, for a total of 16.6 per cent bilaterality.

Table 4 demonstrates that most cancers detected in the contralateral breast by simultaneous biopsy at time of mastectomy were at an early stage of development. In the private group of patients only 6 per cent (1/16) of the infiltrating cancers detected in this manner had positive axillary nodes, while 63 per cent of the contralateral cancers detected were at the noninfiltrating in situ stage. Extent of disease was more advanced in the 20 patients who had previously undergone mastectomy and who were biopsied on the basis of minimal findings detected on follow-up examination. Positive lymph nodes were found in 27 per cent (4/15) of patients with infiltrating cancers, and only 25 per cent of the second cancers detected were treated during their noninfiltrating stage.

A comparable improvement in detection of early breast cancer was noted in the clinic patients whose lesions were detected by contralateral breast biopsy at the time of initial mastectomy. Since October 1965, 289 Memorial clinic patients have been treated for primary breast cancer; 66 per cent of the cancers detected in the contralateral breast at the time of primary surgery were at the noninfiltrating in situ stage, while two of six patients with infiltrating cancer had positive axillary nodes. In the patients who had undergone mastectomy previously and who were biopsied on the basis of minimal findings detected at follow-up examination, 50 per cent of infiltrating cancers detected in the second breast were accompanied by axillary node involvement, while only 20 per cent of the second primary cancers were at the noninfiltrating in situ stage. In this latter group of patients the second cancers were at approximately the same stage of development as the cancers previously treated in the opposite breast.

Table 5 includes all the simultaneous bilateral breast cancers which were detected in our own patients during the last 10 years. All patients were treated by bilateral mastectomies, simultaneous or during the same period of hospitalization. Of the 53 patients, 34 had infiltrating cancer in either one or both breasts, while 19 had only in situ noninfiltrating cancer in both breasts. Almost all cancers detected in the opposite breast by contralateral biopsy of patients treated primarily for in situ noninfiltrating cancer were at the same stage of development. On the other hand, in patients undergoing surgery for infiltrating breast cancer, approximately half the contralateral cancers found were noninfiltrating and half were infiltrating. There were 42 second primary lesions detected on the basis of minimal physical signs, while 11 were picked up by random biopsy—eight of the latter being noninfiltrating lesions.

Table 5. *Simultaneous Bilateral Breast Cancer (1958 to 1968)*

No. of cases	Dominant Cancer	Opposite Breast	Biopsy: Minimal signs	Random Biopsy	X-ray Mammogram	‡	±	0
19	In situ-Non-infiltrating	→ In situ-Non-infiltrating	14	5	10	2	4	4
1	In situ-Non-infiltrating	→ Infiltrating	1		1		1	
16	Infiltrating	→ In situ Non-infiltrating	13	3	6	1	1	4
17	Infiltrating	→ Infiltrating	(*8) 14	3	4	3		1
53	34 with infiltrating cancer 19 only in situ non-infiltrating		42	11	21	6	6	9

* Both cancers diagnosed by physical exam.

Current Status		Less than 5 yrs.	More than 5 yrs.
47	- Living and well	37	10
1	- Alive with disease		1
5	- Dead of disease	4	1
53		41	12

Mammography has contributed moderately to the detection of occult contralateral lesions. Only 21 patients in this group were examined by x-ray mammography. In six instances both breasts were considered suspicious for carcinoma, in six only one side was considered suspicious for carcinoma, and in nine patients there were no x-ray signs of carcinoma in either breast.

The presence of bilateral breast cancer does not carry a hopeless prognosis. Forty-seven of these 53 patients are living and well, one is

Table 6. *Relative Incidence of Bilateral Cancer of Various Types (1966 to 1968)*

No. of pts.	Dominant Cancer	Previous Mastectomy		(non-infilt) Ca	Simultaneous Bilateral Cancer		(non-infilt.) Ca	Bilateral Breast Cancer		(non-infilt.) Ca
264	Infilt. duct	25	9.5%	(1)	22	8.5%	(13)	47	18%	(14)
26	In situ lobular	4	16.0%	(2)	10	38.0%	(9)	14	54%	(11)
16	Non-infilt. intraductile	3	19.0%	(1)	0	0	0	3	19%	(1)
15	Infilt. lobular	0	0	0	2	13.0%	(2)	2	13%	(2)
8	Medullary	1	12.5%	0	1	12.5%	0	2	25%	0
4	Paget's (early)	0	0	0	0	0	0	0	0	0
3	Colloid	0	0	0	1		(1)	1		(1)
1	Adenoid cystic	0	0	0	0	0	0	0	0	0
337	Both breasts biopsied	33	9.7%	(4)	36	10.7%	(25)	69	20.4%	(29)
*505	Total group		6%			7%			13%	

*(168 contralateral breast not biopsied)

alive with disease, and 5 are dead. Twelve patients were treated more than 5 years ago; 10 are living and well, one is alive with disease, and one is dead. Aggressive surgery is indicated when primary cancer is found in both breasts.

An attempt was made to evaluate the relative incidence of bilaterality for various pathologic types of breast cancer in all patients treated for this disease on the Breast Service between January 1966 and August 1968. The "dominant" cancers tabulated in Table 6 comprise cancers found in the second breast of the asynchronous bilateral group plus the dominant lesions noted in the simultaneous bilateral group. No significant difference in bilaterality was found among the various types of carcinomas, except that the in situ lobular carcinomas showed a 54 per cent rate of bilaterality; all others had approximately 20 per cent bilaterality. It should be noted that these data are based upon a total of 337 patients, all of whom had had biopsy of both breasts either by simultaneous biopsy of the contralateral breast at the time of mastectomy or because they were being treated for a second lesion after having undergone a previous mastectomy. The opposite breast had not been biopsied in the remaining 168 patients of the over-all group of 505. The general incidence of bilaterality in the selected group in which both breasts were biopsied was approximately 20 per cent. This dropped to 13 per cent in the over-all group.

SUMMARY

Every effort should be made to detect cancer of the breast at its earliest stage of development, since the prognosis is directly proportional to the extent of the disease at the time of treatment. In general, any persistent dominant mass in the breast should be excised for pathologic examination, even if it appears to be benign. A significant number of apparently benign lesions have been demonstrated through excisional biopsy to be early breast cancers, which have a better prognosis than the average clinically suspected breast cancer. A persistent mass in the breast is best removed even when one is not in doubt of its benignancy. X-ray mammography has contributed to the detection of early breast cancer by demonstrating the need for biopsy, in some instances, before the appearance of physical signs. A suspicious mammogram must lead to surgical exploration of the breast, but a negative mammogram should be disregarded in the presence of a persistent mass in the breast.

In certain carefully selected situations in which there is a high risk of breast cancer, generous biopsy of the breast is justified even in the absence of physical and x-ray signs. This would include patients with a strong family history of breast cancer, with equivocal x-ray findings, with atypical lesions detected by biopsy of the breast, and particularly, patients with proven cancer in one breast. In the latter group, biopsy of the contralateral breast at the time of definitive treatment for a proven breast cancer has demonstrated the presence of occult breast cancer in approximately 10 per cent of the contralateral breasts. These lesions are at a relatively early stage of development, are more localized, and have

a better prognosis, than if they had not been detected and treated until the appearance of definite clinical signs.

Surgical biopsy of the contralateral breast is a minor procedure which is well accepted by the patient. When a positive biopsy is obtained, a second therapeutic mastectomy is more readily accepted than a prophylactic simple mastectomy would be, since the majority of contralateral breasts are free of cancer. Biopsy of the contralateral breast represents a practical approach to the problem of bilateral breast cancer. A negative contralateral breast biopsy does not rule out the possibility of later development of a new primary lesion. All patients undergoing mastectomy for breast cancer must be followed closely with particular emphasis on careful examination of the remaining breast.

REFERENCES

1. Bloodgood, J. C.: The remaining breast after radical removal of the opposite side for cancer. J. South. Surg. Assoc., *34*:223, 1921.
2. Farrow, J. H.: Bilateral mammary cancer. Cancer, *9*:1182, 1956.
3. Foote, F. W., Jr., and Stewart, F. W.: Comparative studies of cancerous vs. noncancerous breasts. Ann. Surg., *121*:6, 197, 1945.
4. Haagensen, C. D.: Carcinoma of the Breast, A Monograph for the Physician. New York, American Cancer Society, 1950.
5. Hubbard, T. B., Jr.: Nonsimultaneous bilateral carcinoma of the breast. Surgery, *34*:706, 1953.
6. Jenson, C. B., Shanon, D. B., and Wangensteen, O. H.: Evaluation of annual examinations in the detection of cancer. J.A.M.A., *174*:1783, 1960.
7. Leis, H. P., Jr., Mersheimer, W. L., Black, N. N., et al.: The second breast. N.Y. State J. Med., *65*:2460, 1965.
8. Newman, W.: In situ lobular carcinoma of the breast. Report of 26 women with 32 cancers. Ann. Surg., *157*:591, 1963.
9. Pack, G. T.: Argument for bilateral mastectomy. Surgery, *29*:929, 1951.
10. Robbins, G. F., and Berg, S. W.: Bilateral primary breast cancers: A prospective clinicopathological study. Cancer, *17*:1501, 1964.
11. Urban. J. A.: Treatment of early cancer of the breast. Postgrad. Med., *27*:383, 1960.
12. Urban, J. A.: Excision of the major duct system of the breast. Cancer, *16*:516, 1963.
13. Urban, J. A.: Evaluation of newer techniques of treatment for breast cancer. Clin. Obstet. Gynec., *9*:235, 1966.
14. Urban, J. A.: Bilaterality of cancer of the breast: Biopsy of the opposite breast. Cancer, *20*:1867, 1967.

Breast Reconstruction

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It is only in this century and especially in the last 20 or 30 years that the cancer patient has been taken out of the "back room," brought into the open wards of hospitals, and allowed to mix with other patients. The stigma of having cancer has faded. Special services as well as specialty hospitals have been organized to treat patients with neoplastic diseases.

We have now entered a second phase in the treatment of cancer. This adopts the philosophy that cancer is a chronic disease and that the patient suffering from it should be given as much help and encouragement as the patient with any other form of chronic disease. With this philosophy in mind, the Plastic and Reconstructive Surgery Service at Memorial Sloan-Kettering Cancer Center has attempted to bring to the forefront the necessity of reconstructing and rehabilitating the patient with malignant disease. Rehabilitation could follow any of the standard modalities of treatment, such as surgery, x-ray, or chemotherapy. The importance of functional rehabilitation is most significant, followed closely by psychological rehabilitation, and then by cosmetic restoration. We have attempted to carry out this work in a number of areas of the body.

No one would argue with the concept that the patient who has had a leg amputation should be fitted with a prosthesis and rehabilitated as soon as possible. This applies not only for traumatic amputation, but even when an extremity is removed because of a tumor. We believe most would agree that even if metastasis is present, the patient should be fitted with a prosthesis and rehabilitated so that the remaining weeks, months, or years can be more comfortable. We have come to the realization that the woman undergoing radical mastectomy or the woman with a deformed breast is entitled to the same treatment. Perhaps here the

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functional and cosmetic components of reconstruction are not nearly as important as psychological rehabilitation.

PRINCIPLES OF RECONSTRUCTION

Methods of reconstruction of the female breast have remained standard throughout the years. Free fat grafts and free fat–dermal grafts have been used in the attempt to enlarge the breasts or to equalize them.[1, 5, 25] While early cosmetic results are acceptable, the free grafts tend to liquefy and disappear, in large part, leaving scarred breasts which are usually of unequal size. Local flaps of dermis and subcutaneous fat have also been advocated for enlarging or equalizing breasts.[17–21] Unfortunately, the amount of tissue present is usually insufficient to carry out the desired reconstruction.

Tubes and flaps from a local area or from a distance have been used to reconstruct a totally absent breast or one removed because of malignant disease. This usually necessitates a number of staged delays, and the surgery itself produces scars in other parts of the body. The length of time needed for reconstruction of a breast might well reach one year.

The method of reconstructing one breast by making use of a portion of the other has also been devised.[1, 11] This is possible only when the remaining breast is large. Statistics show that once a woman has undergone radical mastectomy for malignancy in one breast, the possibility of having a lesion in the other breast is significantly increased. The wisdom of carrying out this type of surgery, therefore, is questionable. Foreign substances to increase the bulk of the breast have been tried throughout the years. These include paraffin, bone, cartilage and various alloplastic materials.[6, 7, 11] Recently, injectable silicone has also been used. All of these substances have been discarded as being useless or producing problems at a later time. Injectable silicone may even be dangerous, and the Food and Drug Administration has banned its use for breast augmentation until further investigative work is carried out.[3, 24]

The Cronin implant as manufactured by the Dow Corning Corp. has proved to be the most useful implant available today.[10, 16] This is a silicone bag filled with liquid silicone, shaped like a breast and available in a number of sizes. It has a synthetic textile mesh backing to help it adhere to the chest wall.

Recently another type of prosthesis has been brought out, consisting of a synthetic plastic bag which is inflatable with a Dextran solution. This allows for variations in size of the two breasts and even the possibility of adjusting the size later.[2]

CLINICAL APPLICATIONS

Unequal Breasts

Breasts may be unequal for a number of reasons. Simple idiopathic hypoplasia of one breast occurs occasionally. Hypoplasia of one breast might be produced by trauma. Treatment of tumors such as hemangiomas by x-ray therapy will frequently destroy the growth potential of a

breast. As the child grows, one breast develops while the other does not. Past puberty, the unequal breast becomes a source of severe embarrassment. The child uses every excuse not to undress in the school locker room and avoids her friends as much as possible. Reconstruction of these breasts can be carried out after the child is fully developed.

One must evaluate the relative disproportion of the breasts, and a number of solutions are possible. If the smaller of the two breasts is adequate in size, the larger breast may be reduced to match it. If the smaller breast is too small, then it must be built up. The method of choice today is the use of a silicone prosthesis (Cronin implant) to increase the size of the smaller breast. If the other breast then remains too large, it can be reduced to bring it into balance. It is to be noted that one cannot promise the patient perfect symmetry of both breasts, but patients must be reminded that no woman has perfectly symmetrical breasts.

Atrophy

A number of women develop progressive atrophy of both breasts after childbirth. They will state that they had good-sized breasts, but that after two or three pregnancies found they had little remaining. The psychological impact of atrophy on these women is frequently severe, and they, too, should be given the opportunity of reconstruction. These women can be helped by bilateral augmentation mammaplasty with silicone implant. The demand for augmentation mammaplasty has increased in recent years, giving the plastic surgeon an excellent opportunity to carefully examine the breast during surgery by means of a bimanual examination: one hand behind the breast and one hand above it.[9, 22] This should be done with every augmentation mammaplasty and any suspicious material removed and examined microscopically. A certain number of malignant lesions are discovered in this manner each year.

Replacement

In certain circumstances it might be well to remove all the breast tissue, leaving the skin envelope and the areola and nipple, and fill the defect with a silicone prosthesis.[13, 15] A patient who has undergone repeated excisions for cysts or for multiple fibroadenomas should be considered a good candidate for this procedure. Once it is established that the patient has chronic cystic disease or multiple fibroadenomas, and the possibility of repeated future excisions is seen, removal of all the breast tissue through a submammary incision should be considered. A silicone prosthesis may then be placed immediately to fill the defect. Alternatively, the wound can be closed and 3 to 4 months allowed to pass so that the tissue can soften before inserting the prosthesis.

Certain cases of large pendulous breasts or ptosed breasts with multiple cysts and fibroadenomas can be treated in a like manner; here it will be necessary to reduce the skin envelope to a more pleasing and suitable size. A silicone implant can then be inserted. It is even possible to consider this type of procedure in certain cases of in situ carcinoma. Figure 1 shows a woman who for a number of years has had repeated ex-

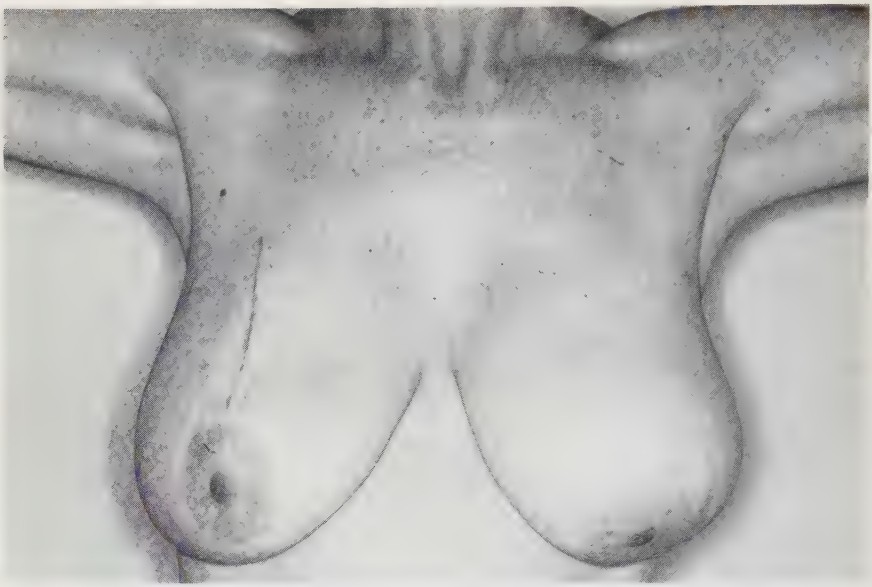

Figure 1. A 47-year-old woman with a long history of multiple cysts and fibroadenomas of right breast requiring repeated excisions. Most recent biopsy showed in situ lobular carcinoma. Patient refused radical mastectomy.

cisions of multiple cysts and fibroadenomas. The latest removal of a nodule showed the presence of an in situ lobular carcinoma. Radical mastectomy was refused by the woman. Figure 2 shows the results following submammary mastectomy leaving the skin, areolae, and nipples intact. Three months were allowed to pass so that the remaining flaps would soften, and Figure 3 shows the result following Cronin silicone implants. A further period of time will be required before final tailoring of the skin envelope. The patient remains free of disease a year and a half after surgery and is extremely pleased with her cosmetic result. Had not this alternative method been offered to her, she would have refused surgery.

In view of the marked fear of mutilation that so many women have, it is unquestionably true that many of them do not seek medical care for breast masses out of fear that a breast will have to be amputated. If thought was given to the possibility of saving more breasts by submammary mastectomy with reconstruction, there is more chance that women would come in earlier for treatment of breast lesions. In addition to benign lesions, as has been shown, it is possible to consider this type of procedure in certain cases of in situ lobular carcinoma. We are aware of the problem of doing an adequate cancer operation through a submammary incision and do not recommend this procedure for an invasive carcinoma. However, all the breast tissue can be removed by this procedure and if frozen section shows invasive carcinoma the operation can always be modified.

In addition, one should consider the possibility of doing a submammary mastectomy on the unaffected breast when radical mastectomy is

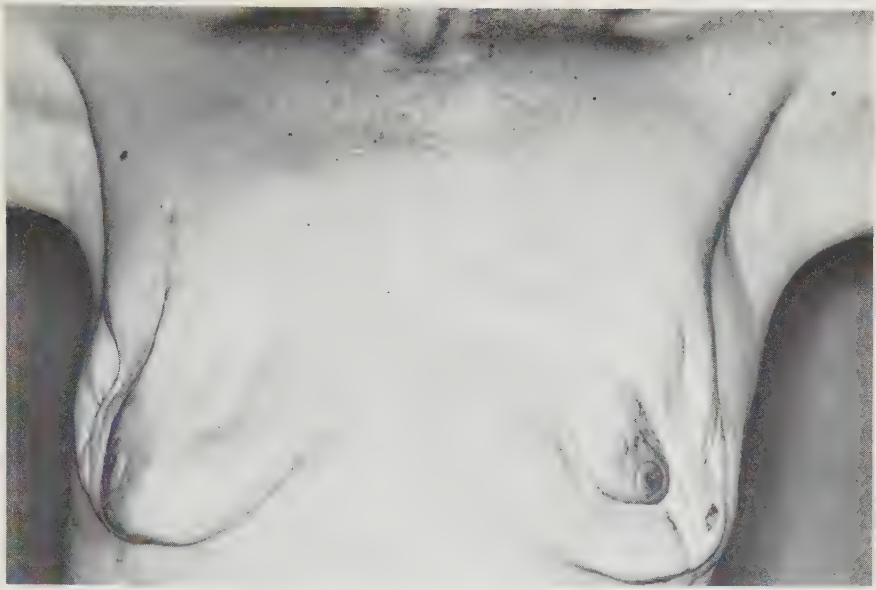

Figure 2. Appearance after bilateral subcutaneous mastectomy. Patient accepted this in lieu of the more radical operation. Prophylactic removal of other breast parenchyma provided an additional advantage.

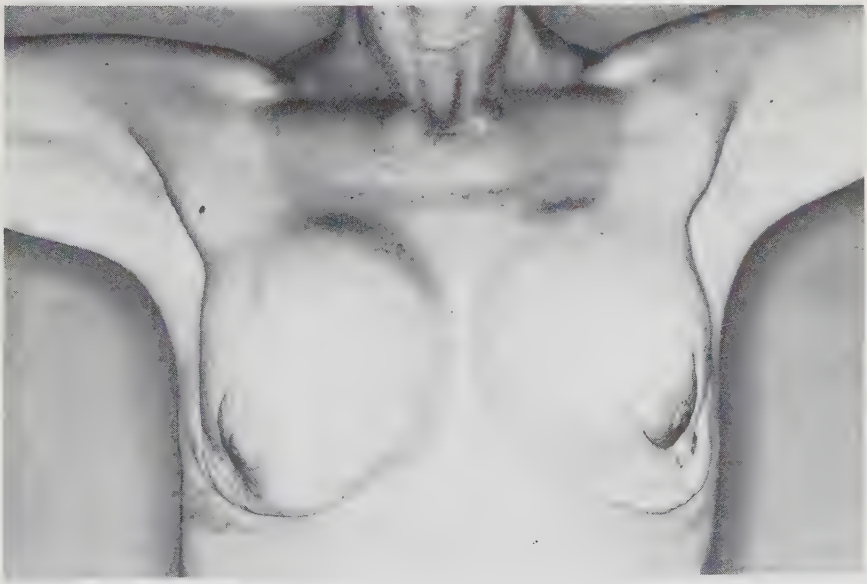

Figure 3. Appearance following insertion of silicone implants 3 months after subcutaneous mastectomy. Patient satisfied with result. Final flap tailoring with free nipple transplant recommended.

carried out. The percentage of malignant lesions in the other breast is high enough to warrant the active consideration of this procedure. More women would be apt to accept this if they realized that they would not lose the bulk and contour of the breast, nor the nipple and areola.

Following Radical Mastectomy

Without question the most severely deformed woman is the one who has had a radical mastectomy. The depression which sets in one or two weeks following a radical mastectomy is well known to all surgeons. At this point many women will inquire about the possibility of having their breasts reconstructed. They should be referred to a competent plastic surgeon, who must explain to them what the possibilities are in the reconstruction of the breast. The surgeon, of course, must consider the type of tumor for which the breast was removed and understand the natural course of the disease. He can give the patient some hope that in the future the breast will be reconstructed, but a period of 6 months should be allowed to pass before any type of reconstruction can be considered. However, the early interview is necessary so as to give the patient the psychological boost that is frequently needed 2 or 3 weeks following a radical mastectomy.

It is to be noted that many of these patients who come in early to ask about reconstruction will finally decide on their own not to have any surgical procedure done. These patients can adjust to the loss of the breast and do not feel that further surgery is needed.

One reason why many women in the past refused reconstruction of the breast was that the procedure outlined to them was prolonged. Frequently it meant rotating a large pedicle flap into the area of the excised breast. This required numerous staged delays. Another method previously used was construction of the tube pedicle, which also took a number of stages to complete. Frequently total reconstruction would take as long as a year. The need for a simpler and more rapid method gave rise to the idea of artificial breast implants. Careful examination of the chest walls in women undergoing radical mastectomy showed in most cases little subcutaneous tissue, but a freely movable covering over the chest wall. Attempts were made, therefore, to elevate a pocket through a low submammary incision. It was found that this could be done without jeopardizing the old scar or causing necrosis of the scar or local tissue flaps. A small implant could then be inserted. The method of insertion and postoperative treatment was similar to that for augmentation mammaplasty. Many of these women developed fluid around the implant which had to be aspirated for a number of weeks. Often the skin flap over the prosthesis was tight, but this gradually stretched as the weeks went by. The immediate psychiatric improvement in these women was amazing, far more than the actual cosmetic improvement. After stretching of the skin, it was possible to remove the small prosthesis and insert a larger one if the patient so desired.

There are two main defects on the woman who has had a radical mastectomy. One is the lack of a mound and the second is a depression in the subclavicular area. Molds are now being developed by the Dow

Corning Company for women who have both defects. The finished prosthesis will be more effective in restoring contour to the entire hemithorax. Some women are concerned only with the subclavicular depression and it is hoped that a prosthesis can be developed just to fill this area.

In no way does the insertion of a silicone prosthesis interfere with the follow-up of the patient for recurrence of tumor. Further, since recurrence frequently does not appear for a long period of time, we believe that the woman is entitled to reconstruction as early as possible.

Occasionally after radical mastectomy and x-ray therapy, x-ray dermatitis and ulceration develop. This patient is also entitled to reconstruction. One may not be able to build a suitable breast in this area, but at least a well-padded flap could be designed and rotated in to replace the devitalized tissue which will frequently consist of not only skin and subcutaneous tissue, but also ribs. It will be hoped that radiation therapy can be planned in such a manner so as to prevent this from occurring. However, even with the best type of irradiation therapy, this occasionally will develop and should be treated as soon as possible; otherwise the sequelae of infected wound and gradual encroachment on the vessels and nerves of the axillary area will occur, leading to edema of the arm and occasionally insufficient blood supply to maintain the limb.

TECHNIQUE FOR INSERTING A SILICONE PROSTHESIS

Silicone prostheses are manufactured by the Dow Corning Corporation, Medical Products Division, and are delivered in a clean envelope. They should never be handled by hand, as an oily film may be placed on the outside of the prosthesis. They are surgically clean and can be sterilized by autoclave or dry heat only. Incisions are made below the normal submammary line through the skin and subcutaneous tissue. The plane of dissection immediately deep to the breast parenchyma is readily found. The dissection can usually best be carried out by a sponge stick and the pocket created should be equal to the size of the prosthesis to be inserted. Hemostasis is essential. The prosthesis should be exposed to the air for a minimal amount of time. Once the prosthesis is in position, it should be carefully checked to make sure that the edges have not rolled under.

The wound is closed in three layers so not to have the edges of the prosthesis pushing into the wound. A simple dressing is used to support the operated side. The patient is kept flat on her back for 48 hours and then gradually allowed to sit up. The elbows should be kept to the sides at all times, and complete use of the arms is restricted for 4 weeks. A brassiere is worn day and night. Antibiotics are given during the stay in the hospital, which is usually 5 to 7 days. Fluid may occasionally develop, especially after radical mastectomy, where there is little subcutaneous tissue present. This can be aspirated by means of a sterile syringe away from the incision and away from the old mastectomy scar. At no time should the breast be allowed to become so tense as to allow rupture of the tissue, especially at the scarred area. Occasionally infection occurs; if after adequate culture and antibiotic therapy this cannot be controlled,

the prosthesis had best be removed. After a suitable interval following resolution of inflammatory reaction, the prosthesis can be reinserted.

PSYCHOLOGICAL ASPECTS

The woman with unequal breasts tends to develop psychological problems.[8, 12] Following a radical mastectomy she frequently feels that she has been mutilated and is no longer a woman. While a good number of these patients will adjust, many of them never do. They may make one or two inquiries of their surgeon concerning the possibility of having the breast reconstructed. Usually they will not be given much encouragement in this direction. Some may be referred for psychiatric help. Unfortunately, a large number of women receive no help whatsoever and drift into their own method of readjustment, which frequently leads to marked difficulties and family unrest. The number of women who have had radical mastectomies and whose family life has been deeply affected cannot possibly be calculated.

While not every woman who has had a radical mastectomy will either be suitable for or desire reconstruction, we believe that whenever a patient shows the slightest interest she should be referred for competent reconstructive surgical advice. In most cases psychiatric evaluation will be of help to these women and to the reconstructive surgeon who must undertake their rehabilitation.

There is no question that the total rehabilitation of the patient who has had a radical mastectomy or other mutilative breast surgery must be encouraged. Separating the woman from her tumor is not the final stage. It is time that cancer be considered a chronic disease like any other chronic disease and every effort be made to rehabilitate the person with cancer in as short a time as possible so that she can make a functional, cosmetic, and psychological adjustment. Every effort must be made to find a suitable and simple method of reconstruction.

SUMMARY

We realize that in this presentation we have raised a number of controversial questions. Should a lesser operation be done on the female breast with a tumor than is now standard procedure in order to leave a woman with a cosmetically acceptable breast and less psychological trauma? Surely there could be no criticism in carrying out a submammary mastectomy for a patient with multiple cysts or fibroadenomas and filling the defect with a silicone implant. The use of this procedure in a case of in situ lobular cancer can well be considered. If this procedure were given more consideration many women would be less fearful in reporting masses in their breast. We believe that this type of surgical procedure should be more widely accepted. The general surgeon should give more attention to the psychologic needs of the woman who has had a radical mastectomy. She should be entitled to a frank and open discussion concerning the possibility of reconstruction. There is no question that the pathological findings must influence this decision. We feel that

the simplest procedure available, the insertion of a silicone implant, while not giving a fine cosmetic result, has been of great psychological benefit to these patients. Carrying out a submammary mastectomy in the other breast with replacement by an implant should also be given consideration.

To date we have no reliable statistics that show any increased incidence of cancer in women who have had silicone implants. There is no question that further vigilance is necessary and long-term follow-up is imperative.

REFERENCES

1. Alexander, J. E., and Block, L. I.: Breast reconstruction following radical mastectomy. Plast. Reconst. Surg., *40*:175-179, 1967.
2. Arion, H. G.: Presentation d'une prosthese retromammaire. Comptes Rendus de la Societé Française de Gynecologie, 35:427-431, 1965.
3. Ashley, F. L., Braley, S., Rees, T. D., Goulian, D., and Ballantyne, D. L., Jr.: The present status of silicone fluid in soft tissue augmentation. Plast. Reconst. Surg., *39*:411-420, 1967.
4. Bames, H. O.: Augmentation mammoplasty by lipo-transplant. Plast. Reconst. Surg., *11*:404, 1953.
5. Berson, M.: Derma-fat transplants used in building up the breasts. Surgery, *15*:451, 1945.
6. Broadbent, R. R., and Woolf, R. M.: Augmentation mammaplasty, Plast. Reconst. Surg., *40*:517-523, 1967.
7. Brown, J. B.: Studies of silicones and Teflon as subcutaneous prostheses (Editorial). Plast. Reconst. Surg., *28*:86-87, 1961.
8. Clarkson, P., and Jeffs, J.: Modern mammaplasty. Brit. J. Plast. Surg., 20:297-310, 1967.
9. Crikelair, G. F., and Malton, D.: Mammoplasty and occult breast malignancy: Case report. Plast. Reconst. Surg., 23:601, 1959.
10. Cronin, T., and Gerow, F. J.: Augmentation mammaplasty: A new "natural feel" prosthesis. Trans. III Internat. Congr. Plastic Surgeons. New York, Excerpta Medica Foundation, 1963.
11. Demergian, V.: Experience with the newer subcutaneous implant materials. Surg. Clin. N. Amer., 43:1313-1321, 1963.
12. Edgerton, M. W., Meyer, E., and Jacobson, W. E.: Augmentation mammaplasty. II. Further surgical and psychiatric evaluation. Plast. Reconst. Surg., 27:279-303, 1961.
13. Freeman, B. S.: Subcutaneous mastectomy for benign breast lesions with immediate or delayed prosthetic replacement. Plast. Reconst. Surg., *30*:676-682, 1962.
14. Harris, H. R.: Automammaplasty. J. Internat. Coll. Surgeons, *12*:827-839, 1949.
15. Kelly, A. P., Jacobson, H. S., et al.: Complications of subcutaneous mastectomy and replacement by the Cronin silastic mammary prosthesis. Plast. Reconst. Surg., *37*: 438-445, 1966.
16. Lewis, J. R.: The augmentation mammaplasty with special reference to alloplastic materials. Plast. Reconst. Surg., *35*:51-59, 1965.
17. Longacre, J. J.: Correction of the hypoplastic breast, with special reference to reconstruction of the "nipple type" breast with local dermo-fat pedicle flaps. Plast. Reconst. Surg., *14*:431, 1954.
18. Longacre, J. J.: Surgical reconstruction of the flat discoid breast. Plast. Reconst. Surg., *17*:358, 1956.
19. Longacre, J. J., DeStefano, G. A., and Holmstrand, K.: Breast reconstruction with local derma and fat pedicle flaps. Plast. Reconst. Surg., *24*:563, 1959.
20. Maliniac, J.: Use of pedicle dermo-fat flap in mammoplasty. Plast. Reconst. Surg., *12*:110, 1953.
21. Marino, H.: Glandular mastectomy: Immediate reconstruction. Plast. Reconst. Surg., *10*:204, 1952.
22. Rees, T. D.: Plastic surgery of the breast. *In* Converse, J. M., ed.: Reconstructive Plastic Surgery. Philadelphia, W. B. Saunders Co., 1964, Vol. 5.
23. Regnault, P. C.: Indications for breast augmentation. Plast. Reconst. Surg., *40*:524-529, 1967.
24. Sadusk, F. J., Jr.: Injection of fluid silicones (Letter to the Editor). Plast. Reconst. Surg., *37*:251, 1966.
25. Watson, J.: Some observations on free fat grafts: With special reference to their use in mammaplasty. Brit. J. Plast. Surg., *12*:263, 1959.

Problems in Chest Wall Resection

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In the resection of chest wall tumors, there are two kinds of problems—first, making the correct diagnosis and performing the appropriate surgical excision (if surgery is indicated), and second, repairing the defect and supporting the patient postoperatively. In major defects, plastic surgical consultation should be sought before the surgical excision, so that the proper reconstruction can be planned and explained to the patient.

The patient who presents with a mass in the chest wall needs thorough, total evaluation. If the chest wall lesion has not already been diagnosed, a diagnosis must be sought by needle aspiration. If the diagnosis is still unknown, the patient will have to be taken to the operating room for a biopsy. If the lesion is small and the defect resulting from complete excision would not be major, excisional biopsy can be carried out. But for a large lesion, incisional biopsy may be preferred, with the operating room prepared for a double set-up just as in the case of "breast biopsy, possible radical mastectomy." Major undiagnosed chest wall masses have about a 50 per cent chance of being malignant. If the diagnosis is not certain on frozen section examination, the surgeon should wait for permanent microscopic section and a final pathologic diagnosis before proceeding with an extensive and possibly mutilating operation.

In case the chest wall has been subjected to heavy doses of radiation therapy, it will ordinarily be necessary to resect back to normal tissue if excision is contemplated. If the surgeon cannot resect back to normal tissue, great caution must be used in operating in heavily radiated and at times infected necrotic areas.

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CONSIDERATIONS OF EXCISION

The type of surgical approach to chest wall resection is dictated by both the anatomic location of the tumor and the cell type of the tumor.

In a lateral chest wall tumor, where ribs are the sole osseous structures involved, excision should be carried out in such a manner that the entire rib segments including the intercostal muscles and the underlying pleura are excised in continuity. At least two normal ribs, one above and one below the tumor mass, are included. It is best to enter the chest cavity through an intercostal space well away from the tumor and examine the interior of the thorax. The ribs are then divided anteriorly and posteriorly with their associated intercostal muscles. A rib involved with tumor should be resected as totally as possible. Neurovascular bundles are carefully ligated and divided. If lung parenchyma is involved, this too is resected. The amount of lung resection depends on the extent of its involvement. The resultant chest wall defect is closed with Marlex mesh. Paradoxical motion and postoperative ventilation problems are usually minimal.

In the lateral chest wall near the superior outlet of the thorax are important anatomic structures, the most notable of which are the subclavian vessels and the lower portion of the brachial plexus. The so-called superior sulcus tumors are primarily cancers of the lung. Carcinomas of the lung in this location may invade the brachial plexus, interfere with the blood supply to the arm or involve the stellate ganglion with resultant Horner's syndrome. They may in addition invade the upper ribs or spine. The most encouraging results to date in the surgical treatment of superior sulcus lesions are where preoperative radiation is followed by surgical excision. The limiting factor in our hands has been the extent of spine involvement. The approach is through a standard posterolateral thoracotomy with mobilization of the scapula. The pleural space is

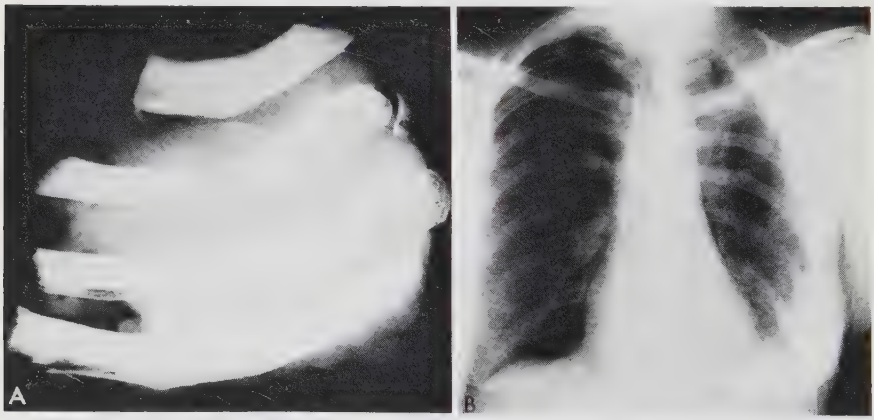

Figure 1. Superior sulcus carcinoma of the left upper lobe, metastatic to ribs 2 and 3. *A*, Surgical specimen. En bloc excision of the left upper lobe and involved chest wall plus an additional rib above and below. Scapula and integument spared. *B*, Postoperative x-ray film shows minimal deformity with negligible functional loss. Marlex mesh closed the defect and no special reconstruction was required.

ordinarily entered through the bed of the fifth rib. Segments of the upper three or four ribs with their adjacent intercostal muscles and neurovascular bundles are frequently included in the resection. The resultant chest wall defect poses no problem because of the scapula covering the resected area, although we prefer to close the defect with Marlex mesh. Postoperative respiratory problems are no different than those of a standard thoracotomy, and there is very little external deformity.

Tumors involving the scapula or the soft tissues of the shoulder girdle necessitate a forequarter amputation in continuity with the chest wall resection. The residual bony defect is covered with Marlex mesh or ox fascia. Adequate skin flaps are obtained from the shoulder region itself.

Lesions low in the lateral rib cage involving the diaphragm pose a special problem. Although the chest wall and diaphragm may be widely resected, major reconstructive techniques become necessary to secure adequate closure of and separation of both the pleural and abdominal cavities and to avoid severe paradoxical motion.

Anterior chest wall tumors are frequently in the sternum with extension to adjacent ribs on one or both sides. Extensive resection of the sternum may be carried out in a manner similar to lateral chest wall lesions. The incision over the sternum is placed transversely either below

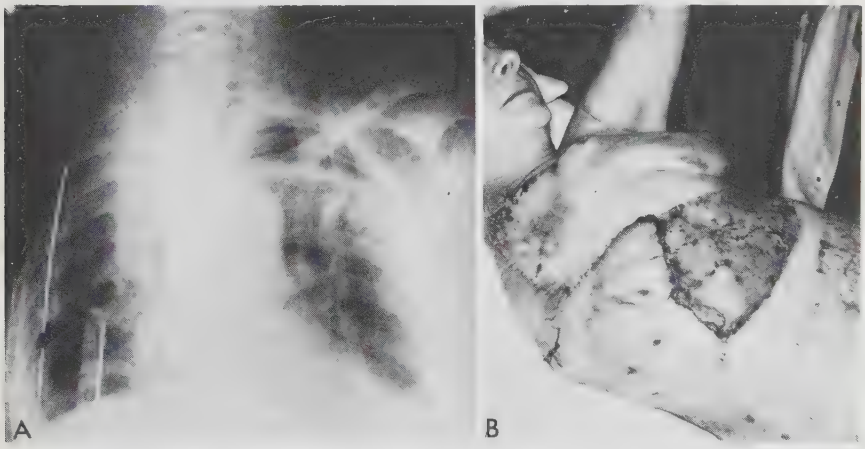

Figure 2. Primary angiosarcoma of the right third metacarpal, radius, ulna, and humerus, involving axillary soft tissue. Right radical mastectomy was done elsewhere 25 years ago for breast cancer and was followed by radiation therapy (exact radiation dose unknown).

Progressive edema and pain in the entire right upper extremity began 1½ years ago. Forequarter amputation was done after bone biopsy 6 months ago was positive for angiosarcoma. Breast cancer did not recur. Chronic ulcer at the apex of the right chest wall developed 4 months ago, with subsequent intermittent, severe hemorrhage. Biopsy showed recurrent angiosarcoma. Chest wall resection was done to excise the residual tumor and control the hemorrhage.

A, Postoperative x-ray film. The resection included the chest wall, encompassing upper three ribs subtotally with the adherent apex of the lung. Iodine-125 seeds were implanted in the base of the neck. *B*, Appearance 1 week postoperatively. The chest wall defect was reconstructed with a massive unipedicle thoracoabdominal flap incorporating the breast. There was minimal paradox with no other reconstruction.

or above the presenting tumor mass and extended first to one and then to the other pleural space as necessary. Changes in the approach are often necessary because of reconstructive considerations.

Lesions in or near the upper third of the sternum may necessitate resection of segments of the clavicle on one or both sides. Similarly, lesions near the xiphoid angle may require interruption of the lower costal arch. Unless the entire sternum is grossly involved by tumor, an effort is made to conserve part of it with its attachment to the remaining rib cage. Severe paradoxical motion is a serious problem with major anterior chest wall resections. It is especially serious whenever bilateral paradoxical motion may result. In these situations every effort is made to maintain the circumferential continuity of the thoracic cage. Reconstruction of the residual defect constitutes a major component of this procedure. Total resection of the sternum if necessary should be staged to secure rigidity by healing of the reconstructed soft tissue. Total sternal resection in one stage is dangerous, and the patient may require permanent ventilatory assistance.

Posterior chest wall lesions. Tumors in the paravertebral region are not readily amenable to wide and complete excision. Parts of vertebral bodies with their laminae and transverse processes have occasionally been resected in continuity with posterior chest wall lesions. Major amounts of the spine can hardly be resected. In situations where surgical removal was incomplete our policy has been to implant the residual tumor with radon seeds. Paradoxical motion and closure of the bony defect do not constitute significant problems in resection of posterior chest wall tumors.

PRINCIPLES OF RECONSTRUCTION

In reconstructive surgery the missing structures should be reproduced in all their elements. Function is restored most effectively when the structure is renewed most accurately.

Chest wall resection for cancer involves excision of a large block of parietal pleura together with the elements of the skeleton. Excision of the overlying integument greatly compounds the reconstructive problem. From the standpoint of reconstructive surgery the definition of what constitutes a major chest wall defect is important. Most chest wall resections for cancer produce minor chest wall defects, but a small anatomic defect can be a major physiologic problem in a poor risk patient.

The following examples of excision usually require only a minor range of reconstruction:

1. Excision of limited chest wall tumors.
2. Radical mastectomies including chest wall resection of the internal mammary chain.
3. Extended resections of intrathoracic tumors with minor sacrifice of the chest wall or hemidiaphragm.
4. Extended resections of upper abdominal tumors with minor sacrifice of the chest wall or hemidiaphragm.
5. Extended forequarter amputation with minor sacrifice of the contiguous chest wall.

6. Extended neck dissections with minor sacrifice of the chest wall.

In all these resections, enough integumentary and bony structures remain that reconstruction can be effected essentially by wound coaptation. Specialized techniques either are not necessary or are minor.

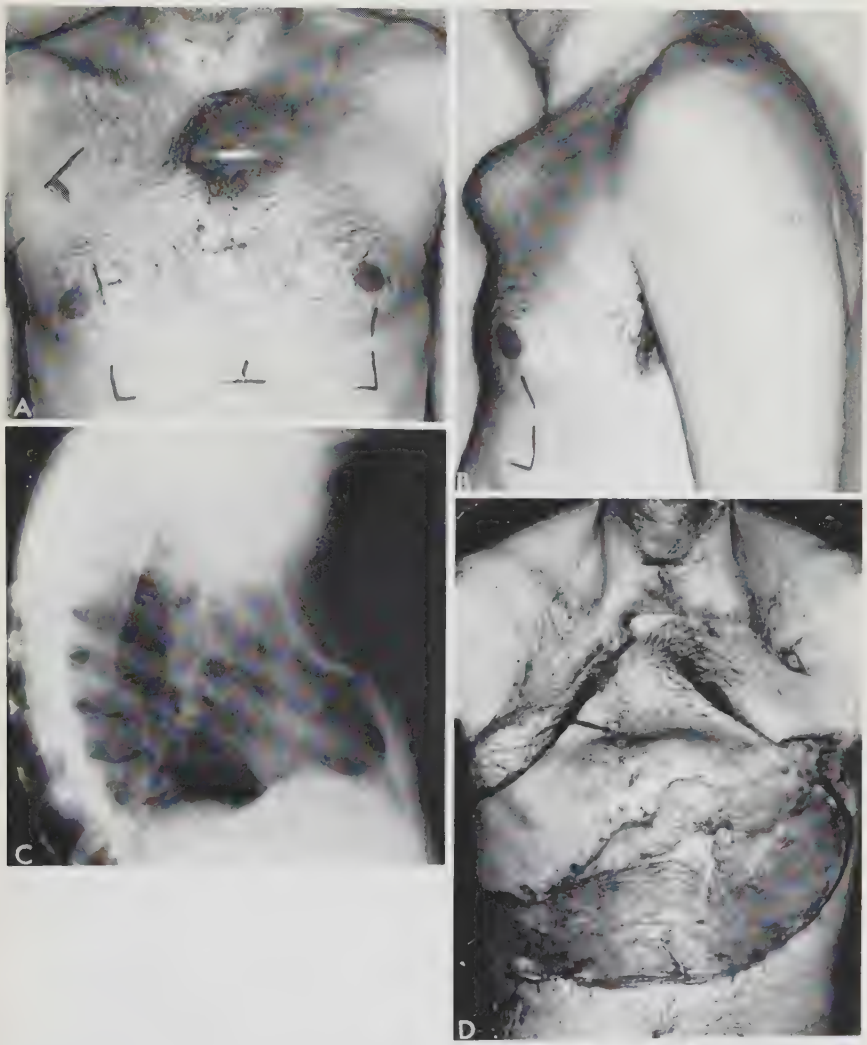

Figure 3. Papillary adenocarcinoma of the left adrenal with a single bulky metastasis to the upper sternum, occupying the anterior mediastinum and protruding through the manubrium. It was biopsied elsewhere. The overlying skin was thin and about to ulcerate.

A and *B*, Preoperative photographs. The tumor protrudes through the chest wall *C*, Postoperative x-ray film. The resection included the entire manubrium, the upper three sternebrae, the upper four costal cartilages and rib ends on both sides, as well as the medial third of both clavicles. The adherent right upper lobe was wedged out en bloc, together with the lower segments of the strap and sternocleidomastoid muscles on both sides. The tumor could be dissected off the fibrous pericardium and the great vessels. The tracheostomy wound did not communicate with the chest wound.

D, Appearance 3 months after resection. The chest wall defect, 20 cm. in diameter was occluded with a single layer of Marlex mesh (Davol Rubber Co., Providence, R.I.) and covered with a massive bipedicle flap from the upper abdomen and lower chest. The flap donor site was split grafted. Moderate paradox required assisted respiration with a ventilator for 2 weeks postoperatively.

Major chest wall defects are more extensive, and require specialized techniques for their reconstruction. This elementary distinction is not always made.[3, 7, 34, 40]

In major chest wall defects four categories of tissue loss can be listed:

1. Integumentary loss only.
2. Skeletal loss only, including parietal pleura.
3. Combined integumentary and skeletal loss.
4. Any of the above categories plus major diaphragmatic loss.

These distinctions are of more than academic interest. Full realization of the extent of all categories of tissue loss is necessary before reconstruction can be planned. In those cases marked by extreme tissue loss, it is mandatory to determine *before* excision whether reconstruction is feasible. This requires accurate planning in three dimensions prior to excision. It is the responsibility of the reconstructive surgeon to help plan all incisions through integumentary and skeletal planes in such a way as to preserve tissue vital to adequate reconstruction. It is also the responsibility of the reconstructive surgeon to judge, during the course of resection, whether or not excision is being held within the bounds of reconstructive feasibility. If excision must exceed this limit, the fact must be recognized before the point of no return, and further surgery must be abandoned. Otherwise the patient will die from respiratory failure or linger on the ventilator. In practice, two types of patients are concerned. One requires extensive resection of the chest wall and diaphragm, and the other requires major resection of the sternum.

TECHNIQUES OF RECONSTRUCTION

The following listing is suggested as a procedural outline with the understanding that the judgment has already been made that reconstruction is feasible.

1. *Determination of the extent of the anatomic defect* with special reference to integumentary and skeletal planes. This should establish an accurate three-dimensional assessment of tissue loss. Attention should be fixed on this problem of tissue loss until insight is gained regarding methods of reconstruction. This process is hard to define, but it is necessary.

2. *Evaluation of the compromise in respiratory function.* This establishes a baseline for use as reconstruction proceeds.

3. *Selective analysis of alternative methods of wound closure.* A permanently closed chest must be achieved. Whatever methods of reconstruction are followed, wound closure must be achieved ultimately by means of full thickness, viable integument. This requires the use of suitable skin flaps. Specifically excluded are flaps of any other tissue, whether parietal pleura, fibrous pericardium, or muscle.[11, 23] These latter tissues have been used in conjunction with split skin grafts to obtain wound closure. Their use is rejected on the grounds that the resulting chest wall cover lacks sufficient stability, rigidity, and viability. In general, proper skin flaps are obtained from the abdominal wall, the back,

or the residual chest. Since most flaps must be unipedicle and undelayed, it is essential to orient their longitudinal axis parallel to their vascular supply, chiefly from the posterior intercostal, the internal mammary perforating, the acromiothoracic, and the lateral thoracic vascular branches. Whether the configuration is that of a transposed, advancement, rotation, or combination flap depends upon the individual situation. In any case, viability must be assured by scrupulous attention to the flap dimension.

Wherever possible, it is wise to use a bipedicle flap designed to insure tip viability. The bipedicle design lends itself best to the situation where flap transfer involves a right-angled change in plane, as in reconstruction of the diaphragm. Use of the female breast is very helpful as a source of large amounts of flap tissue.[37, 47] If the clinical situation allows time for preliminary flap delay, the use of a closed carried flap from the abdomen, attached to the forearm as an intermediate carrier, should be considered for high median chest wall cover.[12] Where the area surrounding prospective flap transfer is avascular, especially following heavy dosage of radiation, the use of a permanent blood-bearing flap is advisable.[9] The late complications of high-dosage ionizing radiation, as is used for re-

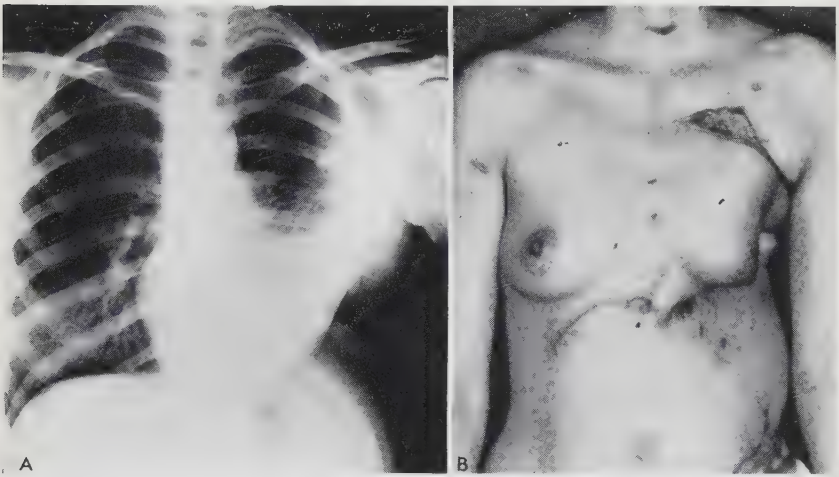

Figure 4. Osteogenic sarcoma in the left sixth rib anterolaterally, with extensive contiguous soft tissue infiltration involving most of the left hemidiaphragm and adjacent pleura.

A, Postoperative x-ray film. A preliminary exploratory laparotomy and thoracotomy were performed to determine operability. The resection included full thickness of the chest wall over a triangular area extending from the third intercostal space in the anterior axillary line to the xiphoid process anteriorly, and to the ninth rib near its angle posteriorly. The specimen included the entire costal margin with a cuff of full thickness abdominal wall, and about 90% of the left hemidiaphragm plus all parietal pleura below the third rib. The tracheostomy wound did not communicate with the chest wound.

B, Appearance 10 weeks after resection. The abdominal cavity was occluded and the hemidiaphragm reconstructed by a massive bipedicle flap comprising the entire abdominal integument below the laparotomy incision. The triangular chest wall defect was occluded by a single layer of Marlex mesh. The chest wall was constructed by a second massive bipedicle flap comprising all the integument above the thoracotomy incision short of the axilla and incorporating the entire left breast. Moderate paradox required assisted respiration with a ventilator for 2 weeks postoperatively.

current breast cancer, are severe and often thwart reconstructive effort.[12, 29, 36, 37, 39]

4. *Evaluation of the need for skeletal plane reconstruction.* It is to be emphasized that the decision to reconstruct the skeletal plane is made only after detailed plans for integumentary closure have been made. This decision, therefore, is made in addition to and entirely apart from the plans for skin flap closure. It should be remembered that restoration of the skeletal plane as a separate anatomical element may not be necessary. Some surgeons always re-establish the anatomic continuity of the skeletal plane as a separate layer, others never do.[7, 12, 29, 36, 42] Reconstruction of the skeletal plane per se is not necessary except for due cause. The compelling reasons are considered to be four in number: (1) when it is mandatory to get sufficient chest wall fixation in a vulnerable area for vital respiratory effort;[8, 19] (2) when it is essential to get additional chest wall fixation in a vulnerable area for more adequate respiratory function;[6, 25] (3) when it is necessary to provide added support for the heart or lung; and (4) when it is advisable to stiffen the chest wall in a large defect to reduce paradox.[5, 16, 22] To this may be added a relative indication: to secure optimal chest wall structure and function in a vigorous patient with long life expectancy.

5. *Selection of the method of skeletal plane reconstruction.* This entails three considerations: first, the degree of functional restoration necessary; second, the status of respiratory function; third, the choice of method designed to best make up the difference. When defect and functional loss are small, repair by local tissues is best. For this purpose, techniques using rib[24] or periosteal flaps or both[32] have long been in use. If the defect is somewhat larger, autologous fascia lata[46] or cutis[2] grafts should be considered; their use is limited, however, by availability, increased operating time, and morbidity. For all practical purposes, therefore, skeletal plane reconstruction involves the use of some foreign material. Theoretically, allogeneic grafts (homografts) are preferable if available. Xenogeneic grafts (heterografts) and sheets of many synthetic materials, such as Marlex mesh,[16, 17, 22] are widely accepted.

POSTOPERATIVE CARE

Postoperatively the major consideration is the care of chest incisions and the support of respiration as indicated. The need for respiratory support is calculated by measuring the tidal volume and analyzing arterial blood gases. If in doubt, the surgeon should support the respiration by a tracheostomy and respirator. The airway should be kept sterile. The respiratory support is discontinued when it is no longer needed.

The illustrations depict four patients who have had their chest walls reconstructed. The photographs express better than words why chest wall reconstruction is a major problem requiring careful planning and close cooperation between thoracic and plastic surgeons.

REFERENCES

1. Adkins, P. C.: The chest wall. *In* Blades, B. B., ed.: Surgical Diseases of the Chest. 2nd ed. St. Louis, C. V. Mosby Co., 1966.
2. Ali, M.: Cutis strip and patch repair of large inguinal hernias. New Eng. J. Med., *251*:932, 1954.
3. Ballinger, W. F., II: The thoracic wall. *In* Gibbon, J. H., ed.: Surgery of the Chest. Philadelphia, W. B. Saunders Co., 1962.
4. Baue, J. O.: Total resection of the sternum. J. Thorac. Cardiov. Surg., *45*:559, 1963.
5. Beardsley, J. M.: Use of tantalum plate when resecting large areas of chest wall. J. Thoracic Surg., *19*:444, 1950.
6. Bisgard, J. D., and Swenson, J. A.: Tumors of sternum: Report of a case with special operative technique. Arch. Surg., *56*:570, 1948.
7. Blades, B. B., and Paul, J. S.: Chest wall tumors. Ann. Surg., *131*:976, 1950.
8. Brodin, H., and Linden, K.: Resection of whole sternum and cartilaginous parts of costae I-IV: Case report. Acta chir. Scandinav., *118*:13, 1959.
9. Brown, J. B., Fryer, M. P., and McDowell, F.: Permanent pedicle blood-carrying flaps for repairing defects in avascular areas. Ann. Surg., *134*:486, 1951.
10. Bryant, L. R.: Mechanical respirators. J.A.M.A., *199*:149-154, 1967.
11. Campbell, D. A.: Reconstruction of the anterior thoracic wall. J. Thoracic Surg., *19*:456, 1950.
12. Converse, J. M., Campbell, R. M., and Watson, W. L.: Repair of large radiation ulcers situated over the heart and brain. Ann. Surg., *133*:95, 1951.
13. Davis, J. S.: Plastic Surgery, It's Principles and Practice. Philadelphia, P. Blakiston's Son & Co., 1919.
14. Dineen, J. P., and Boltax, R.: Problems in the management of chest wall tumor. J. Thorac. Cardiov. Surg., 52:588-594, 1966.
15. Gebauer, P. W., Mason, C. B., Chun, A. K. S., and Connor, M. R.: Prosthesis and autogenous dermal grafts. J. Thorac. Cardiov. Surg., 47:151, 1964.
16. Graham, J., Usher, H., Perry, J. L., and Barkley, H. T.: Marlex mesh as a prosthesis in the repair of thoracic wall defects. Ann. Surg., *151*:469, 1960.
17. Grau, H. R.: Bibliography of foreign substance implants in reconstructive surgery. Addendum No. 2. Plast. Reconst. Surg. Trans. Bull., 29:113, 1962.
18. Grillo, H. C., Greenberg, J. J., and Wilkins, E. W.: Resection of bronchogenic carcinoma involving thoracic wall. J. Thorac. Cardiov. Surg., *51*:447-421 (March), 1966.
19. Griswold, R. A.: Osteochondroma of the sternum: Use of tantalum plate as a prosthesis. Arch. Surg., 55:681, 1947.
20. Griswold, R. A., and Drye, J. C.: Tumors of the chest wall. *In* Pack, G. T., and Ariel, I. M., eds.: Treatment of Cancer and Allied Diseases. 2nd ed. Paul B. Hoeber, Inc., 1960, Vol. IV.
21. Groff, D. B., III, and Adkins, P. C.: Chest wall tumors. Ann. Thorac. Surg., *4*:260-281 (Sept.), 1967.
22. Hardin, C. A., and Kittle, C. F.: Repair of surgical defects of the chest wall. Amer. Surg., 22:139, 1956.
23. Heuer, G. J.: Tumors of the sternum. Ann. Surg., *96*:830, 1932.
24. Janes, R. M.: Primary tumors of the ribs. J. Thoracic Surg., *9*:145, 1939.
25. Kinsella, T. J., White, S. M., and Koucky, R. W.: Two unusual tumors of the sternum. J. Thoracic Surg., *16*:640, 1947.
26. Latham, W. D.: Operative treatment for post-irradiation defects of the chest wall. Amer. Surg., 32:700, 1966.
27. Lavenson, G. S., Jr., and Serfas, L. S.: Advantages of pneumonectomy in massive excision on the chest wall. Amer. J. Surg., *115*:558-563 (April), 1968.
28. Le Roux, B. T.: Maintenance of chest wall stability. Thorax, *19*:397, 1964.
29. Maier, H. C.: The surgical management of large defects of the thoracic wall. Surgery, 22:169, 1947.
30. Maloney, J. V., Jr., Schmutzer, K. J., and Raschke, E.: Paradoxical respiration and "pendelluft." J. Thorac. Cardiov. Surg., *41*:291, 1961.
31. Maurer, E., and Blades, B. B.: Hernia of Lung. J. Thoracic Surg., *15*:77, 1946.
32. Myre, T. T., and Kirklin, J. W.: Resection of tumors of the sternum. Ann. Surg., *144*:1023, 1956.
33. Ochsner, A., Jr., Lucas, G. L., and McFarland, G. B.: Tumors of the thoracic skeleton, review of 134 cases. J. Thorac. Cardiov. Surg., 52:311-321, 1966.
34. Ochsner, A., Jr., and Ochsner, A.: Tumors of the chest wall. Surg. Clin. N. Amer., *46*: 1447-1455, 1966.
35. Odom, J. A., Jr., DeMuth, W. E., Jr., and Blakemore, W. S.: Chest wall chondrosarcoma in youth. J. Thorac. Cardiov. Surg., 50:550-554 (Oct.), 1965.
36. Pickrell, K. L., Baker, H. M., and Collins, J. P.: Reconstructive surgery of the chest wall. Surg. Gynec. Obstet., *84*:465, 1947.

37. Pickrell, K. L., Kelley, J. W., and Marzoni, F. A.: The surgical treatment of recurrent carcinoma of the breast and chest wall. Plast. Reconst. Surg., 3:156, 1948.
38. Ravitch, M. M.: Atypical deformities of the chest wall—absence and deformities of the ribs and costal cartilages. Surgery, 59:438-449, 1966.
39. Snyderman, R. K.: Radiation burns. *In* Converse, J. M., ed.: Reconstructive Plastic Surgery. Philadelphia, W. B. Saunders, Co., 1964.
40. Spear, H. C., Daughtry, D. C., and Chesney, J. G.: Chest wall tumors. Dis. Chest, 37:520, 1960.
41. Staub, E. W., and Beattie, E. J., Jr.: Respiratory support in the postoperative period. SURG. CLIN. N. AMER., 44:227-241, 1964.
42. Sugarbaker, E. D.: Radical mastectomy combined with in-continuity resection of the homolateral internal mammary node chain. Cancer, 6:969, 1953.
43. Urban, J. A.: Radical excision of chest wall for recurring cancer. Cancer, 4:1263, 1951.
44. Vieta, J. O., and Maier, H. C.: Tumors of the sternum: Collective review. Internat. Abst. Surg., *114*:513, 1962.
45. Watkins, N. S., Jr., and Gerard, F. P.: Malignant tumors involving the chest wall. J. Thorac. Cardiov. Surg., 39:117, 1960.
46. Watson, W. L., and James, A. G.: Fascia lata grafts for chest wall defects. J. Thoracic Surg., *16*:399, 1947.
47. Whalen, W. P.: Coverage of thoracic wall defects by a split breast flap. Plast. Reconst. Surg., *12*:65, 1953.

Multiple Primary Cancers, One of Which Is Lung

WILLIAM G. CAHAN, M.D.*

A medical generation ago, when a solitary lung shadow suspected of being cancer was found on the chest x-ray film of a patient who had a known cancer elsewhere in the body, it was assumed to represent a metastasis from the extrathoracic source. Also it seemed reasonable to expect that although the shadow appeared to be single, it actually was the visible representative of a far-flung system of metastases. Thus, there was thought to be little point in aggressive action.

It occurred to several investigators that even if the solitary shadow were a metastasis, it was a unique phenomenon, since metastases to the lung are usually multiple when first observed. They believed that such an unusual clinical setting should be exploited, because some unpredictable beneficial effects might result.[1, 2, 12-14, 19, 22] This concept of aggression was made more plausible by the fact that pulmonary surgery was developing rapidly, and less risk was entailed in removing such lesions. In addition, little else could be offered even as palliation, as most of these lesions were notoriously radiation-insensitive. Although hoped for, cure by excision at that time seemed unlikely.

To the surprise and delight of early investigators, not only good palliation, but in some cases long survival followed the excision of these tumors.[3, 24] Equally unexpected was the fact that the excised lesions frequently proved to be not metastases at all, but separate primary cancers of the lung.[5, 8] Although this seemed at first somewhat of a medical oddity, it nevertheless was quite understandable. Such an occurrence was in keeping with the observation by some that a cancer patient is more "cancer prone" than other patients, and tends to develop new primary cancers 4 to 11 times more frequently. Although others feel that the occurrence of multiple primary cancers of different organ systems is no more than a reflection of the tendency to oncogenesis coincident with aging,[21] they do agree that there is a higher incidence of multiplicity to

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be expected in one organ system, such as the colon, both breasts, oral cavity and pharynx, and larynx and lung. It is reasoned that this frequency reflects the fact that these structures are probably targets for a common carcinogen.

If this predisposition to develop malignant tumors exists, it is reasonable to suppose that as survival rates are extended by a combination of earlier diagnosis and improved methods of treatment, new cancers can be expected to arise at new sites. Physicians dealing with cancer should be on the alert for this possibility, most particularly in the related organ systems.

The wisdom of an aggressive approach to a solitary lung mass was early recognized at Memorial Cancer Center. As a consequence, over 500 histologic specimens in this category have been excised and studied in the past 20 years. It is impressive that at this institution this diagnostic problem arises three or four times a month. It is no longer an oddity and its proper management is an integral part of total cancer patient care.

DIAGNOSIS

Undiagnosed shadows may appear on the chest x-ray film of patients with known cancer, either synchronous with the work-up for the treatment of cancer at another site, or metachronous to the management of the extrathoracic cancer. In either situation, such a lesion warrants a prompt and full investigation concerning its nature and the feasibility of its removal.

HISTORY AND PHYSICAL EXAMINATION. In an attempt to find the nature of the lesion, little help can be derived from the clinical history except for the detailed description and histological review of the extrathoracic cancer. Although primary cancer of the lung may be expected to show earlier evidence of bronchial irritation and stenosis than metastatic cancer, actually they both can be present with these symptoms or with no symptoms, or can mimic other clinical conditions.

A background of prolonged cigarette smoking is influential in suggesting that primary lung cancer exists. Clubbing of the fingers, when found, can be said to be rarely associated with metastases to the lung and suggests primary pulmonary pathology.

A thorough physical examination is necessary with particular search for abnormal lymph nodes, especially those in the supraclavicular areas, and other evidences of metastases.

SEX. Although primary lung cancer of the squamous variety is much more prevalent among men, this fact alone is of no help in distinguishing the nature of a pulmonary opacity in this clinical setting.

AGE. The possibility of a shadow being a new primary lung cancer occurs in patients over 35 years old, since primary pulmonary tumors are rare earlier.

LABORATORY STUDIES. These should be performed as indicated and include liver studies and estimates of cardiopulmonary function, which can influence the decision as to the ability of the patient to withstand excision of lung tissue.

Roentgenographic Studies. The chest x-ray is the most reliable method for indicating intrapulmonary pathology. It is mandatory that proper roentgenographic studies of the chest be made in a cancer patient as part of a complete investigation.

This valuable, easily performed, and relatively inexpensive diagnostic aid is often neglected or incomplete. The sins are usually those of omission. At the time of the initial investigation, or in subsequent detection surveys, a posteroanterior view of the chest may be taken and an accompanying *lateral* view omitted. As a consequence, opacities can be missed, if they are hidden behind the heart shadow or the diaphragms.

In the follow-up examinations of patients whose cancer has been treated, attention will be paid to symptoms and physical findings, but there is often a deficiency in roentgenographic coverage. Chest x-rays may not be taken at regular intervals or may even be omitted entirely until pulmonary symptoms remind the physician to obtain new films. The interval between follow-up chest x-rays must be an arbitrary one. Nevertheless, if they are taken periodically, the chances are improved that early, unsuspected lesions can be detected with a better probability of cure. This is well demonstrated in this series to be presented, since well over half of the pulmonary lesions were found by chance.

In the asymptomatic patient, 6 months is considered by many physicians to be a reasonable interval between chest x-rays, although some prefer one year. This spacing should be shortened when following patients with osteogenic sarcomas, melanomas, or tumors that are notoriously aggressive, or appear histologically aggressive. In these high-risk lesions, appropriate chest x-rays should be taken every 3 months for the first 2 years and at least every 6 months thereafter.

A further error occurs when fluoroscopy[23] alone of the chest, instead of roentgenograms, is used as a screening method. It is difficult to justify such a method which, although useful in studying function, is inexact for studying structures and visualizing small pulmonary opacities. Besides, fluoroscopic images, unless recorded in newer fashions, are impermanent and of no value in determining whether serial changes have taken place. Fluoroscopy exposes the patient to more irradiation than does a roentgenogram and should be saved for when it has specific value.

Once suspicion is aroused by x-rays or by symptoms, proper radiologic evaluation requires several basic studies in addition to the routine posteroanterior and lateral views. These include a stereoscopic posteroanterior (and occasionally, lateral) view of the chest, and fluoroscopy with esophagram. From time to time, oblique views and tomograms may help delineate ill-defined areas, but only rarely do they uncover additional metastases not previously found by the former studies. Special views, such as an apical-lordotic, can be helpful if lesions in the apex are suspected. X-rays of the ribs, cervicothoracic spine, or other osseous areas, using bone detail technique, are done if symptoms or findings warrant.

While these studies are being assembled, a diligent search is begun for previous chest x-rays, as these can prove invaluable as bases for

comparison with the present films. Not infrequently, if the patient is a war veteran, these can be obtained by writing to the Armed Forces at the Federal Records Center. Other possible sources include previous hospital admissions, physicians' offices, employment records, and tuberculosis surveys. However, one should not delay too long while waiting for old x-rays unless these are essential for an understanding of the problem. Such a delay can stretch into weeks and is potentially damaging to a cancer patient.

CYTOLOGY. It has not always been appreciated that cytology derived from sputum and bronchial washings has value in clarifying the nature of metastases to the lung. Burke and Melamed[4] reviewed 100 instances in which tracheobronchial secretions contained cells from metastases. The predominant sources were esophagus, breast, colon, and lymphoma; some of the others were pancreas, kidney, thyroid, and melanoma. Although their study was derived from patients who usually had many metastases to the lung, it has been possible on occasion to obtain diagnostic cytologic information from a solitary lesion, although this is usually difficult in those that are under 2 cm. in diameter. In some instances, in our series, exfoliated cells were identifiable as melanoma, kidney, or testicular cancer, establishing the fact that they were metastases; in others, the cells closely resembled those of a primary lung cancer (larynx, bladder, cervix), so that a distinction had to await analysis of the lung specimen (and even then, an ambiguous result may be obtained). On at least six occasions the lung lesion was readily distinguished as a new primary tumor rather than a metastasis, for the cytology showed squamous cancer and the known extrathoracic tumor was adenocarcinoma.

Bronchoscopic examinations are used to search for and to biopsy endobronchial evidences of tumor, secure cytologic specimens, and to determine whether the extent of the tumor permits excisional surgery. However, this procedure rarely has value for peripherally-placed lesions up to 3 cm. in diameter, and usually is withheld in these settings.

NONSURGICAL MANAGEMENT

When an opacity is discovered under the circumstances that have been described, it is tempting to label such a density with a histologic diagnosis; however, a shadow is just a shadow and it is only by microscopic analysis that a reliable diagnosis can be made.

It cannot be stressed too often that the singleness of the shadow is so rare in this clinical context that one should not only consider a variety of diagnostic possibilities, but also exploit, without too much delay, what may be an unusual expression of the host-cancer relationship.

Such aggression, carrying cautious optimism with it, is at variance with those attitudes, still all too prevalent, that assume the shadow could *only* be a metastasis and probably one of many that are invisible or soon to appear. To those who maintain this view, it seems logical and humane to withhold surgery and instead, to "leave it alone," to "wait and see if

other metastases appear," or to first try irradiation and, more recently, chemotherapy.

In the light of contemporary knowledge, it seems worthwhile to review all of these concepts. It is now apparent that the "leave it alone" school has little to recommend it from the standpoint of diagnosis, therapy, or prognosis, except in unusual circumstances in which the patient is too debilitated to receive any form of therapy.

The "wait and see" attitude is the one most commonly held and has been advocated most often when the deposit is synchronous with the extrathoracic primary cancer or appears a short while thereafter. Such a concept implies that because the extrathoracic cancer has not as yet, or has only recently, been brought under control, no aggressive action should be taken in the face of what would seem to be double jeopardy. It is also reasoned that by allowing an ill-defined interval to elapse, other "metastases" are bound to appear and thus so-called needless surgery would be prevented. (Indeed such an attitude will be rewarded if the delay is long enough!) Here, too, pessimism and waiting serve little purpose in diagnosis and therapy, and particularly, if a synchronous setting exists, may seriously delay and diminish definitive action for either one or both tumors.

Actually, the coexistence of a cancer elsewhere in the body and a shadow in the lung does not exclude the possibility that the latter is a new primary cancer, for in 76 instances this has occurred at this institution (Table 1). In one patient, the concurrent lung shadow proved to be a benign hamartoma instead of a malignant tumor.[18]

By the same token, if an opacity appears metachronously, even as long as 15 years after the control of nonpulmonary cancer (melanoma or fibrosarcoma in this series), it still may be a metastasis.

Radiation therapy has served for years as the mainstay for treating solitary lesions of the lung in this setting. In some instances, a trial

Table 1. *Multiple Primary Cancers, One of Which Is Lung (1933 to 1966)*

OTHER SITES		TOTAL	SYNCHRONOUS	METACHRONOUS
Head and neck		137	36	101
Genitourinary		45	16	29
Breast		22	4	18
Thoracic (Lung and trachea)		19	4	15
Gynecologic		15	3	12
Rectal		16	4	12
Lymphoma		15	2	13*
Gastric		4	2	2
Pancreas		2	2	0
Common bile duct		1	1	0
Bone		2	0	2
Melanoma		2	0	2
Soft part sarcoma		1	0	1
Skin: Basal cell	44	51		
Squamous	7			
	TOTAL	332†		

*Lymphoma under control.
†Without the group having three or more primary cancers (49 cases).

dose of irradiation was given to see if the tumor responded. If it shrank, the dose was carried to higher, usually cancericidal, levels. If no response occurred, surgery was then advised. In other instances, irradiation was administered more as a therapeutic gesture than with the hope that cure could be accomplished. It often provided palliation and had the additional virtue of reassuring the patients and their families that at least "something was being done" for these seemingly hopeless situations. At present, it is administered on the assumption that the shadow is a metastasis and that it might be radioresponsive, as suggested by the known site of origin and cell type. On occasion this assumption proved to be correct, so that there was shrinkage or complete disappearance of lesions arising from the breast, ovary, and testicle, as well as some connective tissue tumors, such as synovioma.

Since the advent of cancer chemotherapy, another nonsurgical method can be tried in those situations in which a possibility of response exists. Certainly, the validity of its being tried in multiple metastases is undisputed. Occasionally it, too, has had value in treating solitary metastases from breast, prostate, testicles, or ovaries, as well as primary cancers of the lung of the oat cell variety and occasionally other tumors. Some of these effects have been augmented by radiation therapy.

But although radiation and chemotherapy, either alone or in combination, occasionally can spare the patient an operation, it must be recalled that these are not without morbidity and hazard and could complicate pulmonary resection if it were embarked upon subsequently. Certain chemical agents can cause systemic symptoms and depress the bone marrow; irradiation, although less worrisome than chemotherapy as an over-all marrow depressant, can cause radiation pneumonitis or fibrosis, increasing postoperative morbidity and reducing pulmonary reserve.

However, more important than these potential dangers is the fact that by trying such nonspecific measures on a supposed problem or diagnosis, a dangerous delay may ensue in instituting definitive treatment, which is only possible when an actual diagnosis is available.

Therefore, in a majority of such situations, either synchronous or metachronous, pulmonary surgery should be considered as an initial step, instead of being relegated to a secondary or tertiary position in the progression of treatment, or employed only as a desperate measure when all else has failed.

SURGICAL MANAGEMENT

In the management of these ambiguous shadows, one can be more easily persuaded to take care of the metachronous lesions, for such a setting permits an estimate of the control of one tumor before making an attack on the other.[7]

However, it was difficult at first to justify surgical intervention when a synchronous setting occurred, because influential early investigators stated that an attack on the pulmonary lesion was defensible only if the extrathoracic cancer was under control. Therefore, they believed

that surgery was indicated only under metachronous conditions, provided that several years had passed between the control of the extrathoracic cancer and the appearance of the lung opacity.

Other observations have modified these early beliefs. For example, solitary metastases from certain organs, such as the kidney, have been removed *before* the discovery and removal of the primary renal tumor, and the patient lived many years thereafter. But, more striking, a synchronously observed pulmonary opacity has proved to be a separate primary lung cancer, and as such could very well be the more lethal of the two.

In this dilemma as to the precedence of procedure for these synchronous cancers, the lung lesion has usually been operated upon after the other cancer. This is attributable, in part, to the fact that the pulmonary lesion was often discovered when the patient had been admitted for definitive surgery on the extrathoracic tumor, and the basic plan for a given procedure was usually maintained. However, this concept should be re-examined. One can use persuasive arguments on both sides of the question of operative priority. For example, if the extrathoracic cancer arises in an abdominal organ, such as the colon or the kidney, a point can be made that at the time of its removal, the liver and other organs within the abdomen can be explored for metastases. If metastases are extensive, there would be no need to explore the pulmonary lesion. As another example, if the extrapulmonary lesion occurs in the breast, it is important to know its exact nature before the pulmonary density itself is investigated, for if this density proves to be a metastasis, this fact would have a direct bearing upon the extent of the excision employed.

On the other hand, lung cancer is very difficult to cure, and its survival figures are below those of breast, colon, and kidney cancers. Therefore, removing this lesion first at least determines whether it is a metastasis, and in any event, its removal may prevent further metastases. Furthermore, excision of the pulmonary lesion permits a fuller inspection of the lung parenchyma, which, if loaded with metastases not roentgenographically observable, might change the nature of the extrathoracic procedure. One further consideration: if the right thoracic cavity is explored, one can palpate the dome of the liver and the right kidney and adrenal areas rather well, which may help to estimate the intra-abdominal spread of cancer. By and large, common sense should dictate priority. For example, if a colon cancer threatened to obstruct, it would warrant a high priority of surgical intervention. On the other hand, a polypoid lesion of the colon found simultaneously with a lung opacity resembling cancer should influence one to give priority to the pulmonary lesion.

Unless aided by presurgical microscopic findings, the surgeon is usually presented with a dilemma as to the nature of the tumor with which he is expected to deal. However, some foreknowledge can be derived in some instances by considering the lung tumor in context with the other known cancer. If, for example, the extrathoracic cancer is an in-situ carcinoma of the larynx or gum, there is little likelihood that

Table 2. *Probable Nature of a Solitary Lung Shadow with Known Cancer Elsewhere (Selected Sites)**

Site of Other Primary CA.	New Lung Primary	Solitary Metastasis	Probable Nature
Hd. & Neck (excluding skin)	137	5	New primary
Breast	22	10	New primary
Trachea & Lung (all types)	19	2	New primary
Prostate	15	0	New primary
Stomach	4	0	New primary
Recto-colon	16	18	Either 1° or met.
Kidney	8	6	Either 1° or met.
Testicle	6	5	Either 1° or met.
Soft parts (SA.)	1	34	Metastasis
Bone (SA.)	2	12	Metastasis
Melanoma	2	17	Metastasis

*Memorial Hospital, 1933 to 1966.

these would metastasize to the lung. Actually, head and neck cancers that have not first metastasized to cervical lymph nodes will rarely spread below the clavicles.[20] Similarly, although a cancer at one edge of a rectal polyp, or an in-situ early cancer of the cervix, are certainly capable of metastasizing to the lung, they would be unlikely to do so in their earlier phases.

In addition to these clues, I derived a rule of thumb that stemmed from a review of many of these cases in 1958 at this institution. It applies to patients approximately 35 years of age or older, for it is largely in this age group that the alternate possibility of a new primary cancer of the lung rather than a metastasis must be considered.

> If the patient has a squamous cancer elsewhere in the body, the solitary lung lesion is usually a separate primary and most likely squamous carcinoma as well. If the patient has an adenocarcinoma elsewhere, there is about an equal chance that the solitary shadow is a primary lung cancer as that it is a metastasis. If the patient has a soft tissue or skeletal sarcoma or a melanoma elsewhere, the solitary lung lesion is most often a metastasis. If the patient has a lymphoma, a solitary parenchymal lesion of the lung is usually a new primary cancer.

In Table 2 these observations are somewhat differently restated. It lists several anatomic areas and the number of new lung primaries or solitary metastases that have arisen from them, indicating in a general way the probabilities of one or the other diagnosis.

At the time of exploratory thoracotomy, a detailed search should be made for evidences of metastases and any spread of cancer to the adjacent organs.

Once excision is decided upon and seems possible, the type of procedure employed will vary with the location of the lesion, the patient's predicted tolerance of the loss of respiratory epithelium, and the surgeon's philosophy. With these variables it is difficult to insist upon any one procedure for lesions in this clinical setting, particularly as there have been long-term survivors following all types of pulmonary resection.

Nevertheless, at this institution certain procedures have seemed more reasonable or logical than others, although, for the present, these can only be considered arbitrary until further data are collected.

With the chest open and the diagnosis still in doubt, tissue may be obtained by excision, incision, or aspiration biopsy. The last two procedures are usually reserved for deep-seated lesions or those centrally located within the lung itself.

If the lesion is peripheral and reasonably small, a wedge excision can be done, which can serve as a diagnostic measure but can under certain circumstances be considered the total procedure. This latter concept is particularly true for metastases from osteogenic and soft tissue sarcomas, melanomas, testicular tumors, and those other cancers in which the histologic characteristics are such as to leave little doubt as to its being from those sources. The value of a wedge excision is its low morbidity and low mortality. An additional virtue is that this group of tumors (melanoma, sarcoma) is notorious for having subsequent pulmonary metastases appear, so that lung parenchyma spared initially in this way can provide functional support should further excisions be necessary. The wedge excisions are also preferred for poor-risk patients, for accessible multiple lesions that are not too numerous, and for the removal of bilateral deposits.[10] Of course, if the lesion is benign, nothing further need be done.

If, however, the pulmonary lesion proves by frozen section to be squamous carcinoma or adenocarcinoma, it is often difficult to determine whether it is a new primary lung tumor or a metastasis, particularly if there is, respectively, a squamous carcinoma or adenocarcinoma elsewhere. In all equivocal situations, but especially in this group, the pathologist should be forewarned to have the sections of the previous cancer available so that he may compare them with the current specimen. Even so, it is impossible to resolve this ambiguity by frozen section examinations; in fact, such a lesion can resist clarification even when more permanent sections are examined. As a consequence, if it can be tolerated, a radical lobectomy is recommended for several reasons: the lobe is an anatomical unit and its removal allows for the possibility that if a primary lung cancer is actually present, a reasonably good margin of non-neoplastic tissue is provided about it; by including the regional lymphatics with the lobectomy, any secondary deposits that may be present in them, either from a primary lung cancer or a metastasis, can also be removed.

However, if the lesion in question involves the main-stem bronchus or extensively involves upper and lower lobes by contiguity, a radical

pneumonectomy[9] may be required for excision.* Here, too, the inclusion of the mediastinal lymph nodes as part of the specimen may remove secondary deposits as well.

Portions of adjacent thoracic structures, such as chest wall or diaphragm, have been excised either by themselves or in combination with adjacent pulmonary tissue, if by so doing the extension and invasion of cancer can be circumvented.[15]

Should surgery prove to be therapeutically inadequate, then other methods could be used subsequently. In fact, at Memorial Hospital, surgery can be an aid to radiation therapy and it is often begun at the time of thoracotomy by inserting radioactive implants into certain unresectable areas.[16] In addition, by three-dimensional observation of the extent of intrathoracic pathology, valuable insight is afforded in planning portal size and position for subsequent external radiation therapy, which roentgenography alone cannot reveal as well. On occasion at operation the intrathoracic cancer is found to be more extensive than originally supposed, so that radiation therapy, which might otherwise have been used, is considered to be futile and abandoned entirely, thereby eliminating needless exposure and expense. Chemotherapy and other palliative measures can be instituted if indicated.

The combination of surgery, radiation therapy, and chemotherapy was used in some instances to improve the chance of cure; in others, in combination, it was expressly used for palliation.

FINDINGS

In studying the results as reflected in the Figures 1 and 2, it is evident that any discussion of one pathologic group in this setting must necessarily overlap and include the other.

Several points are worth stressing. In the first place, there is a preponderance of primary head and neck cancers associated with those of the lung. Of 137 patients in this group, 89 had cancers of the intrinsic and extrinsic larynx. This finding prompted a research program in which patients with laryngectomy were studied at 6-month intervals, at which time they had a cytologic specimen obtained by tracheobronchial lavage, administered through the tracheostomy opening. At the same time, posteroanterior and lateral chest x-rays was taken. As a result of this survey, within 3 years, six cases of primary lung cancer were detected in 308 patients, two of whom had negative chest x-rays; five other patients had metastases to the lung from the larynx; one patient had positive cytology, the source of which is not determined.

In 19 instances, there were two separate primary cancers in the lungs; in 14 of these patients, both were epidermoid carcinomas; in three, both were adenocarcinomas; one had an epidermoid and a terminal bronchiolar carcinoma; and one had an adenocarcinoma and an oat cell carcinoma.

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*The use of a sleeve resection of a tumor in this category with reimplantation of the bronchial stump can be used on occasion for those patients with poor pulmonary reserve, but it has a high risk feature, from both operative and curative aspects.

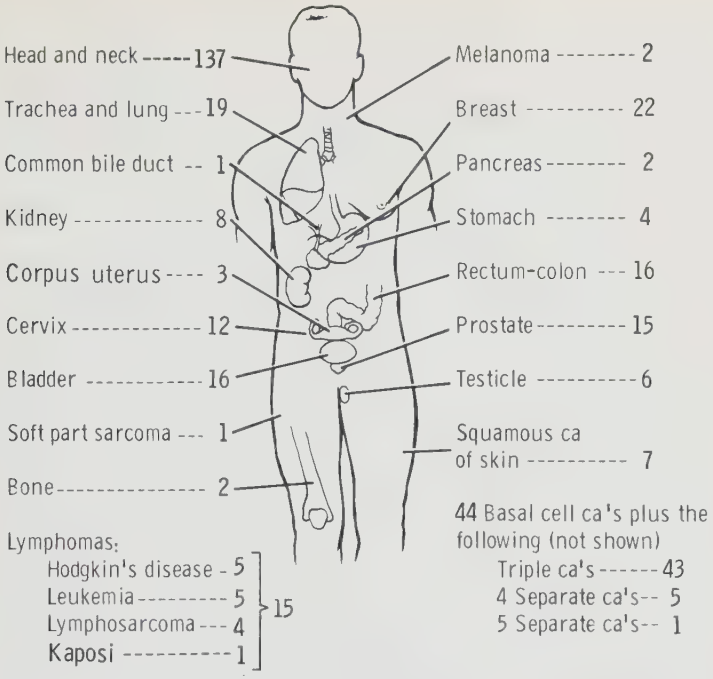

Figure 1. 332 multiple primary cancers, one of which was lung—Memorial Center, 1933 to 1966.

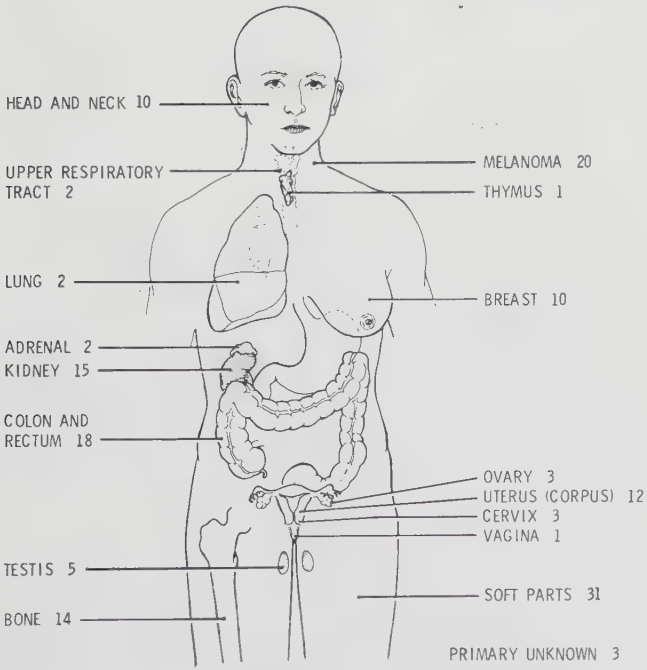

Figure 2. Sources of 153 excised solitary metastases to lung—Memorial Center, 1940 to 1966.

If one studies the diagram, there are some extraordinary expressions of the multiplicity of primary cancers in situations in which it seems highly unlikely that this would occur. Two patients had had melanomas excised previously, and each developed a primary cancer of the lung rather than the expected solitary metastasis. The same may be said about two bone sarcomas and six testicular cancers.

Breast cancers notoriously metastasize to the lung, yet 22 solitary shadows found in this group proved to be new lung cancers rather than metastases. In the same period, there were eight solitary deposits of breast cancer. In two instances, bilateral radical mastectomies had been done for separate primary cancers of the breast, and the lung tumor proved to be a separate primary cancer. One of these patients is alive and well 5 years after the resection of the pulmonary lesion.

Almost all varieties of lymphomas have been seen in this clinical group. When a solitary parenchymal shadow was found in a patient with a lymphoma, the lesion was frequently irradiated under the assumption that it was part of the lymphomatous process. In 15 instances, however, it proved to be a new lung cancer.

As can be seen in Figure 2, there were 153 solitary metastases excised in about the same period. One should note, for example, the infrequency with which head and neck cancers deposit solitary metastases in the lung and the preponderance of those of soft part, colonic, renal, and bone origin. Of the 20 patients from whom melanomas were excised, two have lived 5 or more years.

It is interesting to note that of the 332 patients with multiple primary cancers, 93 had definitive surgery 5 or more years ago. Of this group, 24 (26 per cent) have survived 5 or more years. Of 63 patients in whom a solitary metastasis was excised, 15 (23 per cent) have lived 5 or more years. These figures are quite respectable and about as good as those after excision of primary lung cancer alone.

Finally, there were four instances in which benign lesions were found: two hamartomas, and two granulomas.

In summary, it can be seen that doubt will usually surround the finding of a solitary lung opacity when a cancer exists elsewhere in the body. This doubt can be dispelled by a biopsy, which, at little risk, not only provides a diagnosis, but also permits a concrete basis for management and a better estimate of prognosis. In some instances, excision may be curative; failing this, it may provide palliation.

Such a policy of aggression has made it clearly evident that a situation considered a therapeutic gamble is one no longer. When these enigmatic opacities are encountered, there is little justification for premature defeatism or for delay in their management.

REFERENCES

1. Alexander, J., and Haight, C.: Pulmonary resection for solitary metastatic sarcomas and carcinomas. Surg., Gynec., Obstet., 85:129-146, 1947.
2. Asvall, J., Sanderud, A., and Nitter, L.: Treatment of isolated lung metastases. Acta Radiol. (Stockholm), 6:351-360, 1967.
3. Barney, J. D., and Churchill, E. J.: Adenocarcinoma of the kidney with metastasis to the lung. J. Urology, 42:269-276, 1939.

4. Burke, M. D., and Melamed, M. R.: Exfoliative cytology of metastatic cancer in lung. Acta Cytologica, *12*:61-74, 1968.
5. Cahan, W. G.: Lung cancer associated with cancer primary in other sites. Amer. J. Surg., *89*:494, 1955.
6. Cahan, W. G.: Radical lobectomy. J. Thoracic Surg., *39*:555-572, 1960.
7. Cahan, W. G.: The management of a lung opacity with a primary cancer at another site. *In* Cancer Management. Philadelphia, J. B. Lippincott Co., 1968, pp. 475-483.
8. Cahan, W. G., Butler, F. S., Watson, W. L., and Pool, J. L.: Multiple cancers: Primary in the lung and other sites. J. Thoracic Surg., *20*:335, 1950.
9. Cahan, W. G., Watson, W. L., and Pool, J. L.: Radical pneumonectomy. J. Thoracic Surg., *22*:449, 1951.
10. Cliffton, E. E., and Pool, J. L.: Treatment of lung metastases in children with combined therapy. J. Thoracic Cardiov. Surg., *54*:403-421, 1967.
11. Cliffton, E. E., Das Gupta, T., and Pool, J. L.: Bilateral pulmonary resection for primary or metastatic lung cancer. Cancer, *17*:86-94, 1964.
12. Effler, D. B., and Blades, B.: Surgical treatment of the solitary lung metastasis. J. Thoracic Surg., *17*:27-37, 1948.
13. Ehrenhaft, J. L.: Pulmonary resection for metastatic lesions. Arch. Surg., *63*:826, 1951.
14. Ehrenhaft, J. L., Lawrence, M. S., and Sensenig, D. M.: Pulmonary resection for metastatic lesions. Arch. Surg., *77*:606, 1958.
15. Grabstald, H.: Renal cell cancer. N.Y. State J. Med., *64*:2359-2782, 1964.
16. Henschke, U. K., Hilaris, B. S., and Pool, J. L.: Interstitial implantation of radioactive seeds during thoracotomy for primary lung cancer. Amer. Radium Soc. meeting, Miami, April 1968.
17. Lattimer, J. K., and Conway, G. F.: The place of surgery in Wilms' tumors. J.A.M.A., *204*:127-128, 1968.
18. Mandani, M. A., Dafoe, C. S., and Ross, C. A.: Multiple hamartoma of the lung. Thorax, *21*:468-472, 1966.
19. Maier, H. C., and Taylor, H. C.: Metastatic chorioepithelioma of the lungs treated by lobectomy. Amer. J. Obstet. Gynec., *53*:674-677, 1946.
20. Martin, H., and Braund, R.: Distant metastases in cancer of the upper respiratory and alimentary tracts. Surg., Gynec., Obstet., *73*:63, 1941.
21. Moertel, C. G., Andersen, H. A., and Baggenstoss, A. H.: The coexistence of primary lung cancer and other primary malignant neoplasms. Dis. Chest, *35*:343-347, 1959.
22. Seiler, H. H., Clagett, O. T., and McDonald, J. R.: Pulmonary resection for metastatic malignant lesions. J. Thoracic Surg., *19*:655-679, 1950.
23. Sherman, R. S., and Cahan, W. G.: Isolated fluoroscopy: An evaluation. New Eng. J. Med., *259*:622, 1958.
24. Smith, F. R.: Resection of solitary metastases. J. Int. Coll. Surg., *40*:696, 1963.

Renal Cell Tumors

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During the 20-year period from 1949 to the present, 356 patients have been seen with renal cell tumors at this institution. A major part of my discussion relating to therapy is based on this clinical material.

The surgical treatment of renal cell cancer will be discussed under three categories: (1) without demonstrable metastasis; (2) with an apparently solitary metastasis; and (3) with multiple (defined simply as more than one) metastases. Finally, four special aspects of renal parenchymal tumors will be briefly reviewed: (1) patterns of dissemination and prognosis; (2) the clinically manifest "benign" cortical adenoma; (3) tumor involving the solitary or sole functioning kidney; and (4) renal cell cancer in children.

While a discussion of diagnostic criteria is not pertinent to this paper, certain remarks appear warranted. First, the term "protean" indeed does apply to the renal cell cancer. It is the only tumor which in man or in lower animals is capable of doing all of the following: producing (1) an erythropoietic substance, (2) a parathormone-like substance, (3) possibly a pyrogen, and (4) possibly lactic dehydrogenase and alkaline phosphatase; and of causing (1) hyperproteinemia—usually an elevation in the globulin fraction, (2) a leukemoid reaction, and (3) amyloidosis.[8, 12]

I have recently performed a nephrectomy for renal cell cancer in a woman with multiple myeloma. Renal cell carcinoma is the most common of the abdominal tumors which may produce thrombosis of the inferior vena cava.[21] Furthermore, it is capable of remaining localized for many years, and of metastasizing many years after nephrectomy.[8]

Most important, if one were to delay until the "classical triad" of hematuria, pain, and mass were apparent, the diagnosis would be missed in most cases. More patients have none than have all of these characteristic symptoms.

There are no diagnostic criteria for the early diagnosis of renal cell cancer. The original enthusiasm for the urine lactic dehydrogenase test as a screening test for the diagnosis of asymptomatic renal cell cancers has waned. In our experience, it has not proved worthwhile in the diagnosis of any tumor.

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SURGICAL TREATMENT

Two-thirds of patients with renal cell cancers have no metastases at the time of diagnosis. Only 1.7 per cent have a solitary metastasis, and 27 per cent have multiple metastases initially. In 4 per cent, renal cell cancer is an incidental autopsy finding.[19]

The Patient with No Metastases

Comments on surgery may be prefaced by stating that there are no therapeutic alternatives superior to the simple removal of the primary. Radiation therapy may or may not have an adjunctive role, and there are no consistently useful chemotherapeutic agents.

The objective of a surgical program may be cure or palliation. While we recognize the sometimes long natural history of apparently localized renal cell cancer and the inability to predict clinical behavior in the individual case, nephrectomy is still advocated. Morbidity and operative mortality rates are low. Nephrectomy is recommended with due recognition of the fact that "cure" or long-term survival (merely a matter of semantics) may not be clearly attributable to the procedure.

Knowledge of what to remove depends, obviously, upon an understanding of the mode of spread of the tumor. When speaking of "radical nephrectomy" one must also consider therapeutic alternatives.

TUMOR GRADE, RENAL VEIN, AND VENA CAVA. Carter emphasized, among other factors, survival according to grade and renal vein involvement.[5] He noted that grade I tumors are more frequently localized within the kidney and not often associated with renal vein invasion. Conversely, the incidence of extrarenal spread and renal vein involvement is higher in grade 3 tumors, and the 5-year survival rates are lower. Riches' 5-year and 10-year survival figures are 75 per cent and 44 per cent in low-grade tumors when the renal vein is not invaded, and 33 per cent and 16 per cent respectively when the vein is not invaded with high-grade tumors. Further, when the vein *is* invaded, the 5-year and 10-year survival figures are 50 per cent and 20 per cent for low-grade tumors and 20 per cent and 19 per cent for high-grade tumors.[24] Even though this series is small, results indicate that efforts should be made to remove the entire renal vein and, obviously, the tumor thrombus. In our series, gross vein invasion and local extension were noted to be less ominous than lymphatic metastases. Early pedicle ligation is more talked about than accomplished, but such is the aim.

Tumor thrombi were found in the renal vein in 54 per cent of the patients in an early series,[18] only 29 per cent of whom survived for 5 years, as compared with 55.4 per cent who lived for 5 years when the renal vein was not invaded. This difference serves to further emphasize the need for careful examination of the renal vein and the vena cava, as involvement was only 9 per cent (14 of 152) in one series.[1] Renal vein involvement might well correlate with existence of distant metastases at the time of initial diagnosis.

RENAL AND TUMOR CAPSULE, PERIRENAL FAT, AND FASCIA. The fibrous capsule was involved in the majority of cases in one series, with or without perirenal fat or venous involvement.[3] In 75 of these 343 cases,

only the capsule was involved. Perirenal extension was noted in only 9 per cent in another series.[14] Removal of perirenal fat and fascia (Gerota's), and obviously of renal and tumor capsule, are inherent mandatory aspects of a good "radical" procedure and add little to the operating time or morbidity. Opening the peritoneum near the colon and working both within the peritoneal cavity and retroperitoneally may facilitate this added removal of fat and fascia. In a properly done radical nephrectomy, the tumor per se may not be seen until it is off the field.

Nodes. Metastases to regional lymph nodes have been described in some 5 to 38 per cent of patients in various reports.[14, 17, 23] Adequate knowledge of lymphatic distribution is not available, because systematic node dissection has not been routinely performed in most series. The extent of desirable node dissection is yet to be defined, but a reasonable approach would be to dissect nodes around the renal pedicle, possibly to a level as low as the inferior mesenteric artery and above to the diaphragm. Involved nodes are most likely to be within this area.[10]

The report of Robson and our experience suggest that radical nephrectomy may be preferable to simple nephrectomy. Robson believes that an improvement in prognosis results from the removal of nodes (involved in 22 per cent of patients), early pedicle ligation, and removal of fat and fascia with the kidney. He had a 66.3 per cent over-all 5-year survival rate.[26] Certainly the possibility of more effective local control of tumor growth appears justified, especially since morbidity and mortality are not increased with the radical procedure. There is much to suggest, however, that the determining factors in the patient with a more favorable prognosis are more likely to be the natural history of the disease and the stage and grade of the tumor than the radical surgery.

Choice of incision is arbitrary and may well depend upon the training of the surgeon, especially if he is to consider a thoracoabdominal or a transperitoneal approach for an en bloc dissection of a multivisceral tumor mass, such as renal cell cancer invading the large bowel.[8] Other factors may include tumor size, body build, and pulmonary status, especially if one wants to consider a concomitant ipsilateral chest exploration.

The Patient with a Solitary Metastasis

Two factors might justify a vigorous surgical approach to the patient with a solitary metastasis from renal cell cancer. The first is proof that this is seen frequently enough to warrant concern. Second, the results must justify the surgery, taking into account the occasional need for rather extensive and potentially "mutilating" operative intervention for the purpose of removing a presumed solitary metastasis. The latter procedures include such operations as shoulder girdle disarticulation[8] and brain surgery.[19]

Barney and Churchill's case report of a patient who successfully underwent nephrectomy and resection of a single pulmonary metastasis was the first such case reported, and it stimulated the interest of others to seek similar problems.[2] Just how often, however, does one see the renal cell cancer patient with a solitary metastasis? It is rare indeed; of 482 cases, only eight (1.7 per cent) had a solitary metastasis.[19]

Recently, Fallon and Roper reviewed 299 cases with pulmonary metastatic disease from various primary sources. Only 24 (8 per cent) had solitary metastases.[7] There were no primary tumors of the kidney in this group.

One would conclude, therefore, that while the problem is admittedly rare, it does exist. That being the case, one must next turn to a study of the results of management, hopefully to justify enthusiasm for this way of coping with the problem.

In Fallon's series, 6 of 24 patients (25 per cent) survived 5 years after treatment of primary and pulmonary metastatic disease.[7] In Middleton's series, four of eight patients died within the first year.[19] The other four are interesting. One is alive over 17 years after brain surgery for metastasis and 31 years after the nephrectomy. The 14-year interval between nephrectomy and the development of the brain metastasis might well be the real clue to this patient's successful management—that is, the tumor's slow growth pattern. The three other patients in this group developed other metastases 1, 2½, and 4 years later.

Of 59 patients, 45 per cent survived at least 3 years and 34 per cent at least 5 years after removal of the metastasis and proof of its renal cell origin.[19] These survival (? cure) statistics are about the same as those in patients without metastasis. This would suggest one conclusion: any renal cell tumor nice enough to go to one select spot is indeed a well-behaved tumor.

The problem of differentiating a solitary metastasis to one kidney from new renal cell primary in the opposite kidney needs to be discussed. It is of interest that the reported incidence of renal cell tumors in solitary (or sole functioning) kidneys is the same as that reported of solitary metastasis to the thyroid gland.[11, 13] This provocative finding lends much weight to the argument that a second renal cell primary is conceivably a metastasis.

The vigor with which one ought to pursue a metastasis obviously depends upon its location. One might easily consider removing a rib or a lung lobe for a solitary metastasis, yet justifiably hesitate to suggest brain exploration or shoulder girdle disarticulation under the same circumstances. Among the factors to be considered are the age and general condition of the patient, the interval between discovery of the primary and finding its metastasis, and the grade of the tumor.

A small measure of success has been achieved in the management of five patients with solitary metastases involving the humerus in two cases and the shoulder, rib, and lung in one each. The three patients alive at the time of my report in 1964 remain alive and free of disease. Two patients are alive and free of demonstrable disease over 6 and 8 years after renal surgery and shoulder disarticulations.[8]

Figure 1 shows one of these patients whose solitary humerus lesion did not respond to radiation and whose symptoms demanded disarticulation.

Two final facts bear emphasis before critical interpretation of these "good results" reported following removal of tumor and solitary metastasis. First, most of these 5-year survivors (? cures) still die of metastatic

disease. Second, one wonders about the number of many unsuccessful cases not reported as compared with the relatively small series of successful cases reported.

The Patient with Multiple Metastases

In the presence of multiple metastases, nephrectomy may be considered on three bases. (1) As part of a planned approach to remove the primary tumor and to excise or otherwise treat the metastatic disease, it is very rarely feasible. (2) There may be a faint hope that metastases would regress after nephrectomy. This also is, indeed, a rare phenomenon. I have seen regressions of pulmonary metastases in two men after nephrectomy and, in both instances, recurrences, other metastases, and death were noted in less than a year.[8, 9] (3) Nephrectomy may be done for the purpose of palliation of local or systemic symptoms.[8]

Among the many factors to be considered in the evaluation of patients when surgery is to include removal of metastatic disease are histologic tumor type, stage, and grade; size of the primary; size, location, and extent of metastases; and the time between discovery of the primary and recognition of metastases.

In patients with flank pain or hematuria, it is reasonable to assume that nephrectomy would alleviate these local symptoms—but so may radiation therapy. The decision is more difficult, however, if the primary is silent and the metastases are causing symptoms, or when the bulk of the total tumor is outside the kidney. For example, what response may one expect if a primary renal cell cancer weighs only 50 gm. and the metastases weigh much more? Would one be likely to relieve such systemic symptoms as fever, malaise, and anemia when the bulk of the tumor is outside the kidney? How may one justify nephrectomy in this setting? We have arbitrarily suggested that nephrectomy might possibly alleviate systemic symptoms if the bulk of the total cancer is confined to the kidney.

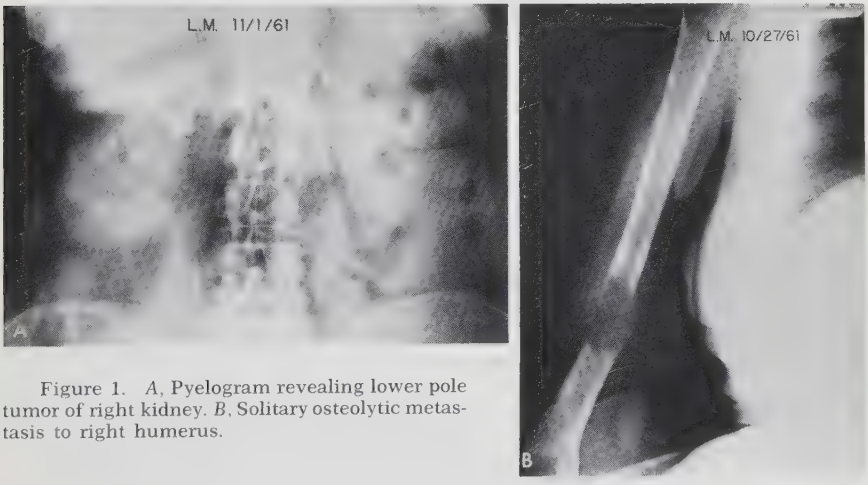

Figure 1. *A*, Pyelogram revealing lower pole tumor of right kidney. *B*, Solitary osteolytic metastasis to right humerus.

Nephrectomy in the presence of widespread metastases may provide symptomatic improvement, but it is not likely to prolong life.[8, 19] Of 30 patients subjected to nephrectomy in the presence of multiple metastases, two lived for 1 year and none survived over 2 years.[19] The results were similar when nephrectomy was omitted.

Clinical judgment still plays a large part in any therapeutic decision. In a patient who is a good risk and who can tolerate nephrectomy, the operation is still offered as a possibility, but it is never urged as a mandatory part of his over-all management.

SPECIAL PROBLEMS

Patterns of Metastasis and Prognosis

Several features of the renal cell cancer contribute to the prognosis of the patient. All constitute an integral part of the nebulous "natural history." Some are measured in the patient and others in the tumor. Age, sex, race, symptoms, and laboratory measurements of urine and blood are to be considered in the patient's evaluation. Regarding the tumor per se, size, calcification, histologic grade, and cell type and stage, in terms of fat, fascia, node, and vein involvement or metastases, are among the objective factors pertaining to prognosis.

The time factor, as it relates to tumor dissemination and prognosis, has been studied. Golbey has reviewed the records of 78 renal cell cancer patients (unpublished data). It was observed that, prior to death, widespread metastasis (defined as to two or more viscera) was almost invariably noted. In fact, death could reasonably be predicted within 6 months of the proof of widespread dissemination. Six dissemination patterns were described.

1. *Early dissemination.* Patients with two or more organs involved by metastases at the time of diagnosis. Their survival was the shortest; one, however, lived for 50 months.

2. *Late dissemination.* These patients had no clinically discernible metastatic disease or only local residual tumor for 3 to 84 months after nephrectomy. When metastases appeared, they were widespread, and the patients died within a few months.

3. *Initial metastases to bone prior to generalized dissemination.* This group survived an average of 27 months from clinical onset to death when bone metastases were present at the time of initial treatment. When, however, the bone metastases appeared later, the mean survival from onset was 121 months and the survival from bone metastases was 35.7 months. These patients also had relatively longer survival after widespread dissemination, averaging 10.7 months.

4. *Initial metastases, intrathoracic, prior to generalized dissemination.* In this group, 3 of 26 did not die with dissemination. Average survival time with chest dissemination at diagnosis was 16 months from clinical onset and 14 months from the diagnosis of pulmonary disease. When intrathoracic disease appeared after a tumor-free period, however, survivals were, on the average, 50 per cent shorter than in patients with bone metastases.

5. *Initial metastases other than to bone or intrathoracic.* These consisted of a small group of patients with miscellaneous metastases whose average survivals were midway between patients with bone and those with intrathoracic lesions.

6. *No metastases.* Three patients died with no dissemination. One died of amyloidosis present for 10 years; the other two died of infection. The average survival was 45 months from onset to death. The range, however, was wide: 5 to 66 months.

The conclusions are that generalized disease must be present before a firm prognosis can be offered and that once it is present, prognosis is firm: poor and relatively unchanged by any therapy.

Cortical Adenoma

Though the term "cortical" is appropriate to designate the histologically benign adenoma, it is not applicable to the malignant renal cell carcinoma, which may involve the medulla as well. Hence, the all-inclusive term "parenchymal" (as distinguished from pelvic) tumors is more appropriate.

The role of adenoma in the genesis, pathogenesis, or growth of the renal cell cancer remains elusive. Possibly it is the precursor of cancer; conceivably its presence is an unrelated phenomenon. Certain studies suggest that their coexistence is more than fortuitous. In 12,885 routine autopsies (25,770 kidneys), adenomas were found in only 33 (0.13 per cent) and carcinomas in 44.[16] Yet, Newcomb found a much higher incidence: 87 adenomas in 2344 kidneys (3.7 per cent).[20] The incidence of adenoma was 4.4 per cent in patients with renal cell cancers; 5.8 per cent in men and 1.3 per cent in women.[6] Thirty-seven adenomas were found in 22 of 567 kidneys removed for Grawitz's tumor. The thoroughness with which one examines specimens undoubtedly alters "incidence" statistics.

It is known that renal cell cancers are found predominantly in men by a ratio of 4:1, yet it is not generally recognized that this same ratio holds true for the adenoma. Not only is the place of the adenoma in the renal cell picture not settled, the role of steroids in the growth of adenomas is also enigmatic. In male hamsters cholesterol esters in the renal tubular epithelium increase with tumor growth, and disappearance of esters is followed by cessation of growth.[15] The clinical significance is uncertain, but it is interesting that diabetes mellitus is often associated with hypercholesteremia and diabetics are apparently more vulnerable to renal cell cancer.[8] Cortical adenomas are also more common in diabetics. Why, also, have virtually all of the so-called responders to any chemotherapy in the literature been men? It is odd that almost all of the "spontaneous regressions" following nephrectomy have also been in men. Malignant and metastasizing adenomas have been produced only in male hamsters, not in females, by the chronic use of estrogens.[15] Conceivably, the induction of tumors in female hamsters is prevented by their natural progesterones. Yet, the tumors may also be produced in female hamsters if estrogens are added, if ovaries are removed at times of low progesterone secretions, or before reproductive maturity.

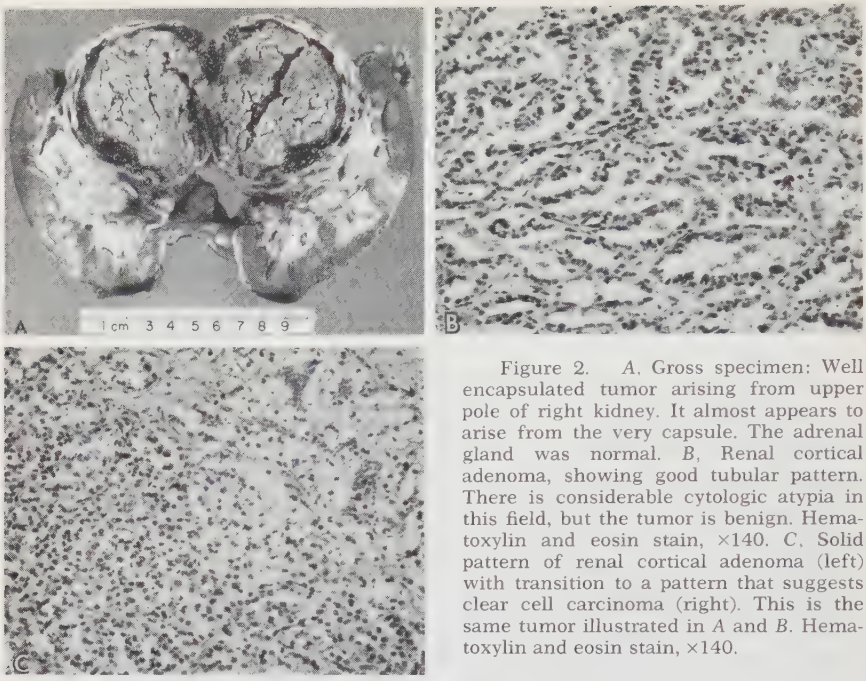

Figure 2. *A*, Gross specimen: Well encapsulated tumor arising from upper pole of right kidney. It almost appears to arise from the very capsule. The adrenal gland was normal. *B*, Renal cortical adenoma, showing good tubular pattern. There is considerable cytologic atypia in this field, but the tumor is benign. Hematoxylin and eosin stain, ×140. *C*, Solid pattern of renal cortical adenoma (left) with transition to a pattern that suggests clear cell carcinoma (right). This is the same tumor illustrated in *A* and *B*. Hematoxylin and eosin stain, ×140.

These isolated facts do not quite "gel" yet, but they may have clinical pertinence when considering Bloom and Wallace's report of favorable response of human renal cell cancer metastases to progesterone or testosterone.[4]

Adenomas which reach "giant" size ("clinically manifest" is more appropriate) are rare, for by this time, the histologic trend of the tumor has been toward recognizable malignancy. Size is not the only criterion, though it is known that tumors under 3 cm. rarely metastasize. It is for this reason only that adenomas over 3 cm. in size are called cancers by some pathologists.

I have previously described a "pure" benign renal cortical adenoma in an adult woman with an associated lung hamartoma.[8] An apparently benign adenoma with areas of transformation to renal cell cancer is pictured in Figure 2. Pyelograms over a 6-year period show the tumor's slow growth pattern (Fig. 3*A* to *E*). Arteriograms demonstrate abnormal vessels around the upper pole, where the tumor appears to arise from the kidney edge and capsule (Fig. 3*F*). The old adage, "if a renal mass increases slowly in size it is likely a cyst" does not hold true.

Renal Cell Cancer in the Solitary or Sole Functioning Kidney

Several features distinguish the patient with renal cell cancer in the only remaining kidney.

1. *Rarity.* Only 45 cases have been collected.[11]

2. *Age.* A high percentage of patients are relatively young. Of the 45 patients, 19 were between 35 and 49 years of age.

3. *Reason for removal of the opposite kidney.* Nineteen of 45 (42 per cent) had previous nephrectomy for renal cell cancer. This introduces the possibility of metastasis.[11] It is a reasonable assumption that a patient with renal cell cancer in the solitary kidney may, indeed, have a solitary metastasis, rather than a new primary. First, the renal cell cancer is peculiar in its propensity to spread as an individual isolated lesion to a unique spot. For example, isolated metastases to the thyroid gland have

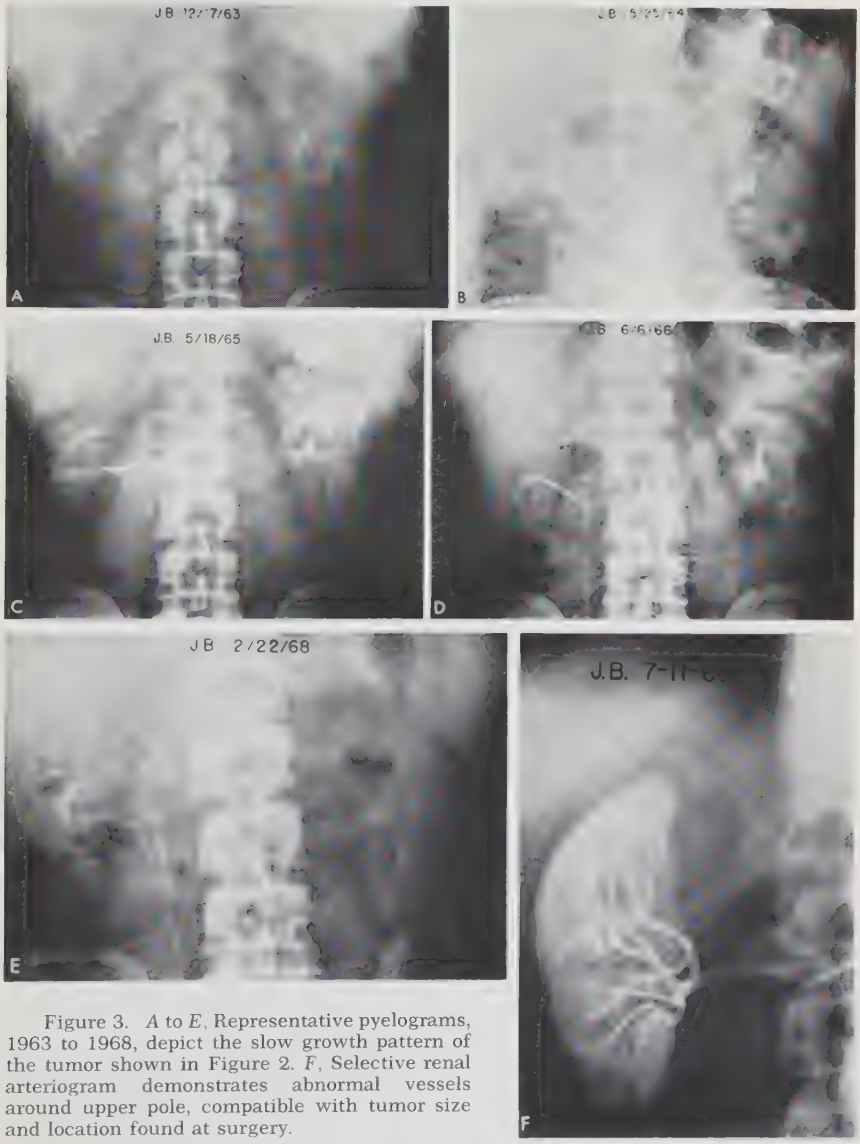

Figure 3. *A* to *E*, Representative pyelograms, 1963 to 1968, depict the slow growth pattern of the tumor shown in Figure 2. *F*, Selective renal arteriogram demonstrates abnormal vessels around upper pole, compatible with tumor size and location found at surgery.

been reported in 49 cases.[13] Spread to isolated, relatively unusual sites without lung involvement is in keeping with this possibility of a solitary metastasis, even years later. The long delay between the recognition of the primary tumor and the development of metastasis is very well known in the renal cell cancer patient.

4. *Interval between nephrectomy and recognition of tumor in remaining kidney.* Periods of 6, 10, 13, 14, 18, and 20 years have elapsed between nephrectomy for one renal cell cancer and the recognition of the new primary (or metastasis).[11] Wound recurrences 8 and 11 years after nephrectomy and without distant metastases have been noted, obviously implying slow growth patterns. This is also in keeping with the possibility of slow growing or delayed metastasis. It also relates to treatment response.

5. *Treatment and results.* Treatment details per se are described elsewhere.[11] I am here more interested in relating the favorable response to treatment, in this most unfavorable setting, to the tumor's behavior. All of the survivors in our review had partial nephrectomy at least as part of their treatment.

Of 30 patients treated only by partial nephrectomy, 23 were rendered free of disease for periods of 1 to over 10 years. All 25 patients free of disease were treated by partial nephrectomy, with or without subsequent or previous treatment. There were no spontaneous regressions in our series, and four patients left untreated died with disease, but with relatively long survivals (24 to 36 months) in three.

The very fact that there has been relative success with partial nephrectomy emphasizes a favorable tumor or patient milieu. One cannot, for example, speak of good ablative cancer surgery in the traditional sense (removal of a tumor by a wide margin) when one excises a solitary kidney tumor and is satisfied with and is able to obtain only a few millimeters margin.

Renal Cell Cancer in Children

Certain features also distinguish this group.

1. *Rarity.* The exact number of reported cases is difficult to interpret because of differences in evaluating criteria of authenticity; 51 cases were collected in 1961.[27]

2. *Age.* This is rather interesting as there is a predominance of older children, aged 7 to 17, a definitely higher age peak than noted with Wilms' tumor. Our four children were 7 to 11 years of age.

3. *Symptoms.* As in adults, the classical triad is rare. Renal mass, hematuria, fever, anemia, and skeletal metastases were noted. A mass has been seen in most, while gross hematuria was infrequent. Because of its rarity, preoperative diagnosis is rarely made.

4. *Results of treatment.* Virtually all had nephrectomy with or without postoperative radiation. Five-year survival figures are unfortunately not available, as most cases have been reported within 3 months to 2 years of treatment. In one report, the authors noted 16 of 43 patients to be dead, one presumed dead, 13 well, and 13 unknown. Only one long-

term survivor was noted, 15 years after nephrectomy.[27] One of our four patients is alive 13 years after nephrectomy.

Four children with renal cell tumors have been seen at this hospital and mentioned in my previous review,[8] but have not been reported in any detail.

Case Reports

Case 1. R.R., age 7, male, whose present illness started with periumbilical and later right flank pain. There was no hematuria. A preoperative diagnosis of Wilms' tumor was made and right nephrectomy was performed. The gross tumor was the "size of a baseball" (about 8 cm.) and occupied the lower portion of the right kidney. Microscopic examination was done by Dr. Fred Stewart, who felt that the diagnosis was consistent with that of clear cell carcinoma. The boy remains free of disease 13 years after nephrectomy.

Case 2. S.L., age 11, female, whose present illness started with weakness, vomiting, headache, blurring of vision, and a neck lump. Symptoms and signs of increased intracranial pressure required craniotomy. Several months later, she first noted gross hematuria. Work-up revealed a right renal tumor and nephrectomy was carried out. She had originally received cobalt treatment to the head, as well as to the right kidney area, although nephrectomy was not carried out until 2 years after craniotomy. Pathologic evaluation was by Dr. Stewart; he noted "patterns suggestive of clear cell carcinoma—more adult in appearance than the true Wilms' tumor." The child was lost to follow-up 6 months after nephrectomy, at which time she was known to have skull metastases.

Case 3. H.R., age 11, male, whose present illness started with epigastric pain, anorexia, and weight loss. On examination, a right flank mass was noted. Chest x-ray revealed multiple pulmonary metastases. Right nephrectomy was carried out and the pulmonary metastases were treated with methotrexate, vincristine, and actinomycin D without response. He subsequently developed metastases in vertebrae, pelvis, and femurs. Scattered radiation therapy for palliative purposes was given to all symptomatic, tumor-bearing areas. The child died 11 months after nephrectomy not having responded to any therapeutic measure. Dr. Robert Hutter diagnosed "clear cell carcinoma of kidney with extension into renal vein." Postmortem examination revealed widespread metastases.

Case 4. P.A., age 11, female, whose present illness started with fever and abdominal pain. A mass was noted four weeks after the onset of fever. Right nephrectomy was carried out, and the result of the pathology examination by Dr. Arthur Allen was "renal adenocarcinoma of adult clear cell and granular cell type." Subsequent radiation therapy was given to the tumor bed. The patient developed scoliosis and areas which were suspicious, but were never confirmed as metastases. Recurrence in the abdominal wall scar was noted 16 months after nephrectomy. Actinomycin D was used without evidence of objective response in the massive local recurrence. Proof of recurrence in the nephrectomy scar was made by aspiration biopsy, and this area was subsequently treated with additional radiation therapy with some decrease in size. She subsequently developed a metastasis in the right femur, 27 months after nephrectomy. Pulmonary metastases increased prior to death, when she was noted to have pleural effusions and, finally, a right hemihemothorax. She died 28 months after nephrectomy.

SUMMARY

A treatment philosophy for renal cell cancer patients without metastases, with solitary, and with multiple metastases is presented. The rarity of solitary metastases is noted, and the futility of nephrectomy in the presence of multiple metastases is emphasized. The over-all reaction pattern of this peculiar tumor with protean manifestations is re-emphasized.

Several isolated problems concerning renal cell cancer are reviewed: (1) patterns of early and late dissemination and prognosis; (2) the enigmatic cortical adenoma as it relates to hormones and the malignant tumor; (3) involvement of solitary or sole functioning kidneys; and (4) renal cell cancer in children.

REFERENCES

1. Arkless, R.: Renal carcinoma: How it metastasizes. Radiology, *84*:496-501 (Mar.), 1965.
2. Barney, J. D., and Churchill, E. J.: Adenocarcinoma of the kidney with metastasis to the lung: Cured by nephrectomy and lobectomy. J. Urol., *42*:269-276 (Sept.), 1939.
3. Beare, J. B., and McDonald, J. R.: Involvement of the renal capsule in surgically removed hypernephroma: A gross and histopathologic study. J. Urol., *61*:857-861 (May), 1949.
4. Bloom, H. J. G., and Wallace, D. M.: Hormones and the kidney: Possible role of testosterone in a patient with regression of metastases from adenocarcinoma. Brit. Med. J., 2:476-480 (Aug.), 1964.
5. Carter, R. L.: The pathology of renal cancer, J.A.M.A., *204*:221-222, 1968.
6. Cristol, D. S., McDonald, J. R., and Emmett, J. L.: Renal adenomas in hypernephromatous kidneys: A study of their incidence, nature and relationship. J. Urol., 55:18-27 (Jan.), 1946.
7. Fallon, R. H., and Roper, C. L.: Operative treatment of metastatic pulmonary cancer. Ann. Surg., *166*:263-265 (Aug.), 1967.
8. Grabstald, H.: Renal cell cancer. N.Y. State J. Med., *64*:2539-2545, 2658-2671, 2771-2782, 1964.
9. Grabstald, H., and Golbey, R.: Clinical experiences with thalidomide in patients with cancer. Clin. Pharmacol. Therap., *6*:298-302 (May-June), 1965.
10. Grabstald, H.: The extent of nephrectomy for renal cell cancer. J.A.M.A., *204*:277-229, 1968.
11. Grabstald, H., and Aviles, E.: Renal cell cancer in the solitary kidney. Cancer, 22:973-986, 1968.
12. Grabstald, H., Murphy, G. P., and Bush, I.: Experimental aspects of renal tumors. *In* Bush, I.: Current Problems in Urologic Investigation. Baltimore, Williams & Wilkins Co., in press.
13. Hedinger, C., Corbate, F., and Eglof, B.: Thyroid metastases of hypernephroma. Schweiz. Med. Wschr., *97*:1420-1426, 1967.
14. Kaufman, J. J., and Mims, M. M.: Tumors of the Kidney. Chicago, Year Book Medical Publishers, Inc., 1966.
15. Kirkman, H., and Bacon, R. L.: Malignant renal tumors in male hamsters (Cricetus auratus) treated with estrogens. Cancer Res., *10*:122-123, 1950.
16. Kozoll, D. D., and Kirshbaum, J. D.: Relationship of benign and malignant hypernephroid tumors of the kidney. J. Urol., *44*:435-449 (Oct.), 1940.
17. Lucke, B., and Schlumberger, H. G.: Tumors of the renal pelvis and ureter. *In* Atlas of Tumor Pathology. Washington, Armed Forces Institute of Pathology, 1957, Fascicle 30, Section 7.
18. McDonald, J. R., and Priestley, J. T.: Malignant tumors of kidney; surgical and prognostic significance of tumor thrombosis of the renal vein. Surg. Gynec. Obstet., 77:295-306 (Sept.), 1943.
19. Middleton, R. G.: Surgery for metastatic renal cell carcinoma. J. Urol., 97:973-977 (June), 1967.
20. Newcomb, W. D.: The search for truth, with special reference to the frequency of gastric ulcer-cancer and the origin of Grawitz tumors of the kidney. Proc. Roy. Soc. Med., *30*: 113-136 (Dec.), 1936.
21. Ney, C.: Thrombosis of the inferior vena cava associated with malignant renal tumors. J. Urol., 55:583-590 (June), 1946.
22. Nourse, M. H., and Yurdin, D. H.: Renal carcinoma in children. J. Urol., *82*:21-25 (July), 1959.
23. Petkovic, S. D.: An anatomical classification of renal tumors in the adult as a basis for prognosis. J. Urol., *81*:618-623 (May), 1959.
24. Riches, E. W.: Analysis of patients with adenocarcinoma in a personal series. *In* Tumors of the Kidney and Ureter. Edinburgh, E. & S. Livingstone, Ltd., 1964, pp. 357-368.
25. Riches, E. W.: The place of irradiation. J.A.M.A., *204*:230-231, 1968.
26. Robson, C. J.: Radical nephrectomy for renal cell carcinoma. J. Urol., *89*:37-42 (Jan.), 1963.
27. Scruggs, C. D., and Ainsworth, T.: Renal cell carcinoma in children: A review of the literature and report of two cases. J. Urol., *86*:728-733 (Dec.), 1961.

The Treatment of Bladder Tumors

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The treatment of bladder tumors occupies an important place in urology, not only because of the relative frequency of the disease, but also because of the continuing efforts to improve its management. Almost 3 per cent of the more than 300,000 cancer deaths in this country in 1968 were due to bladder cancer. The objectives of the present discussion are to illuminate the rationale of the treatment program currently practiced at Memorial Hospital and to inquire into the causes of treatment failure. The end results of treatment of patients with bladder tumors are a function of (1) the nature of the tumor (and the tumor-host relationship), (2) the quality of the treatment effort, and (3) the nature of the treatment.

THE NATURE OF THE TUMOR AND THE TUMOR-HOST RELATIONSHIP

The current dearth of knowledge concerning host factors which condition the behavior of tumors limits characterization of the host to such considerations as age, sex, race, and general health (life expectancy) apart from the presence of the bladder neoplasm. Although considerable information has accumulated concerning a variety of features of bladder tumors, the relevance of each of these features to the behavior of the tumor in a particular host has not been clearly demonstrated. The features may be enumerated without attempting to assess their relative importance to tumor behavior:

(1) Clinical criteria: duration of the history; nature of the symptoms; number and nature of previous treatments.

(2) Gross criteria: location, size, and number of tumors; gross morphologic features of the tumor (e.g., papillary or nonpapillary, sessile or pedunculated, ulcerated or nonulcerated).

From the Department of Surgery

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Table 1. Tumor Grade

Papilloma	Benign
Grade I carcinoma	Low grade
Grade II carcinoma	
Grade III carcinoma	High grade
Grade IV carcinoma	

(3) Histologic criteria: cell type; histologic grade; degree of infiltration of the bladder wall (stage); presence or absence of lymphatic or blood vessel invasion; karyotype.

(4) Biochemical criteria: assessment of the rate of incorporation of tritiated thymidine and tritiated cytidine in DNA and RNA, respectively.

Although it seems quite possible that each of these features, and others yet to be defined, may ultimately warrant a place in a complex equation defining the biologic potential of a particular tumor in a particular host, the need for a simple, accurate, and reproducible method of assessing a tumor has culminated in the adoption of a system in which the pathologic features of grade and stage provide the basis for tumor characterization. The grade of the tumor is determined by the pathologist by histologic examination of a tumor sample (Table 1). Experience has demonstrated that the grade provides an indication of the growth potential of the neoplasm. The tumor stage designates the degree to which the

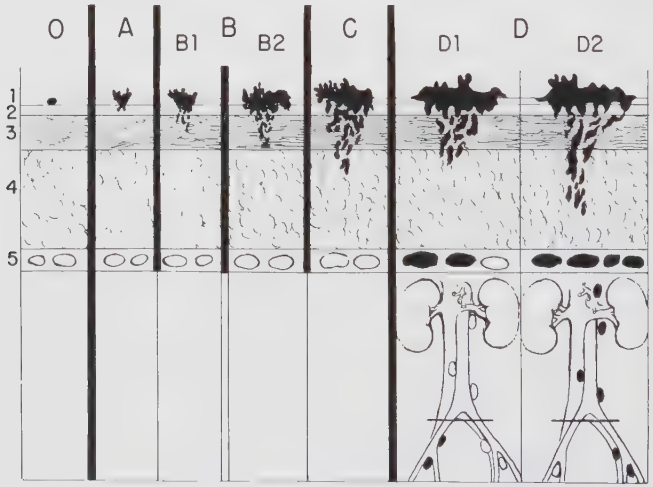

Figure 1. Stages of vesical neoplasms. O, Limited to mucosa; A, not beyond submucosa; B1, not more than halfway through muscle layer; B2, beyond the halfway level of the muscle layer, but not into fat; C, beyond the muscle layer, but not metastatic or invading the substance of adjacent organs; D1, metastatic to the pelvic lymph nodes or invading the substance of adjacent organs; D2, metastatic beyond the pelvis.

Table 2. *A Dual Classification of Vesical Neoplasms*

	Stage						
	Superficial			Deep		Metastatic	
Grade	0	A	B1	B2	C	D1	D2
Papilloma							
Low grade carcinoma							
High grade carcinoma							
Other types							

tumor has penetrated the bladder wall (Fig. 1). Stage may be clinically estimated by the clinician on the basis of cystoscopic and bimanual examinations under anesthesia and from the adjunctive use of intravenous pyelography. Experience over the past 20 years has indicated that the clinical estimate of tumor stage will prove approximately 80 per cent accurate pathologically, relative to whether the tumor is superficially infiltrating or deeply infiltrating, and that there is a greater tendency to underestimate the extent of the tumor than to overestimate it. The accuracy of clinical staging can be enhanced by correlation with information relative to tumor grade and stage obtained from adequate biopsy. The dual pathologic features of grade and stage permit characterization of all bladder tumor experience (Table 2).

An analysis of experience in terms of such a characterization reveals several facts of practical importance to the management of patients and to the validation of the classification. (1) Papilloma, a histologically benign lesion, usually occurs only in a mucosal stage, and its rare occurrence in a deep or metastatic stage is probably a consequence of iatrogenic influence. (2) Low-grade tumors tend to occur in superficial stages, a fact evident from experience with radical surgery, in which approximately two thirds of patients with low-grade carcinomas have lesions which are in superficial stages. (3) By experience too, high-grade lesions tend to occur in deep or metastatic stages. (4) Superficially infiltrating tumors are rarely found in a metastatic stage, a fact evident from: (a) the relatively good results of conservative therapy for low-stage tumors; (b) the observations of Jewett and Strong[17] in autopsied patients with bladder cancer, demonstrating the relationship of tumor stage to theoretical curability by cystectomy; and (c) the rarity (approximately 5 per cent) of lymph node metastasis in patients with superficially infiltrating tumors treated by radical surgery. (5) Deeply infiltrating tumors are associated with a 40 per cent incidence of regional lymph node metastasis.

Several corollaries emerge from these considerations: (1) A low-stage tumor is generally limited to the bladder wall and its local control,

by whatever means, is associated with a theoretically good prospect of control of that particular lesion. (2) A high-stage tumor may or may not be confined to the bladder wall, and the possibility of prior extravesical dissemination, even if the primary tumor is adequately controlled, exposes the patient to an approximately 40 per cent chance of therapeutic failure. (3) The recognized error in clinically estimating whether a given tumor is of low stage or of high stage, the greater probability of underestimating than of overestimating tumor extent, the greater probability of deep infiltration with a high-grade than with a low-grade tumor, and the pathologic difficulties in distinguishing between superficial and deep muscle infiltration, support the concept that *any* evidence of muscle infiltration in the case of a high-grade cancer justifies placing the tumor in the deeply infiltrating category.

QUALITY OF THE TREATMENT EFFORT

Relatively little has been written on this sensitive subject. Even such an indisputable fact as treatment mortality cannot unreservedly be regarded as an indication of the capabilities of the individual rendering the treatment, since it is so dependent upon case selection. The frequent similarity in end results following similar treatments of apparently similar tumors by different treaters suggests an equivalent competence of the different treaters and implies that important differences in end results are more apt to be due to the case selection or to the methods of treatment than to the individual treater's capabilities. Judging from the larger series of patients with bladder tumors reported in the English literature, the degree of competence with which ordinary treatment is ordinarily administered varies surprisingly little.

NATURE OF THE TREATMENT

Although present and future hopes for chemotherapy and immunotherapy in the management of various tumors are not unfounded, the basic skills of surgery and irradiation, with minor exceptions, remain the bulwarks of current bladder tumor treatment. The balance of this discussion will be devoted to a consideration of applications of irradiation and surgery in the management of patients with bladder tumors of so-called "transitional cell" origin.

Surgical Treatment

Endoscopic excision or fulguration. This may involve excision alone, fulguration alone, or combined excision and fulguration. Although the importance of deep excision with the use of a cutting current is frequently emphasized, the theoretical possibilities of tumor dissemination via the lymphatic and blood vessel channels transected during this procedure warrant the use of a coagulating current in conjunction with the cutting current. The use of fulguration alone has been legitimately criticized on the basis of the inability to control accurately the depth of coagulation necrosis produced. Endoscopic methods of therapy are

associated with low mortality and morbidity and are adaptable to multiple applications.

Suprapubic excision or fulguration. Suprapubic techniques may be utilized to accomplish the same ends as endoscopic methods, but they carry greater morbidity, and repeated application to the same patient has obvious practical limitations. The risks of extravesical implantation of tumor with the suprapubic approach have to be weighed against the risks of dissemination fostered by the transection of lymphatic and blood vessel channels in the closed bladder with the hydrostatic relationships prevailing during transurethral procedures. Although the magnitude of the hazards of tumor implantation or dissemination cannot be quantitated from available data, elective transurethral prostatic resection or prostatic enucleation, concomitant with transurethral or suprapubic excision and fulguration of bladder tumors, respectively, is felt to be inadvisable.

Segmental resection. This procedure involves removal of a full-thickness segment of bladder with its contained tumor, varying portions of perivesical fat, overlying peritoneum, and regional lymph nodes. The margin of normal bladder around the periphery of the tumor should never be less than 2 cm. and optimally should be 3 to 4 cm. The operation is generally well tolerated and has a mortality of under 5 per cent. It has the advantage of providing a satisfactory excision of highly selected tumors and of simultaneously preserving normal vesical and sexual function. It has the disadvantage of being ideally applicable only to that small proportion of patients in whom the tumor is solitary without history of tumor elsewhere in the bladder and the tumor is *at least* 2 cm. from the bladder neck.

Simple cystectomy and the other exenterative procedures have the dual theoretical advantages of providing the patient with prophylaxis against other bladder neoplasms and of providing protection for the upper urinary tract against the obstruction and infection which are not uncommon terminal events in uncontrolled bladder tumors. However, these advantages are attained only at the price of a mortality of 10 to 15 per cent and a morbidity of about 50 per cent. Furthermore, the associated inconveniences and risks of urinary diversion, coupled with the loss of sexual function, further detract from the theoretical advantages of such procedures.

Radical cystectomy, which has essentially replaced simple cystectomy at this institution, involves a wider local excision of the bladder than does simple cystectomy, coupled with a systematic dissection of the pelvic lymph nodes, usually as high as the level of the common iliac artery bifurcations.

Pelvic exenteration involves removal of the juxtavesical rectum in conjunction with the bladder and usually entails the need for a colostomy in addition to urinary diversion. The mortality is about 15 per cent. This procedure has been rarely utilized in recent years, because experience has demonstrated that survival rates with bladder tumors of similar stage treated either by radical cystectomy or by pelvic exenteration are essentially the same.

Translumbar amputation has had limited use in the treatment of highly selected patients. Although it seems possible that it will offer prospects of tumor control in otherwise hopeless, selected patients, its limitations as a method of treatment need no elaboration.

Radiation Therapy

Methods of radiation treatment of bladder cancer include interstitial irradiation, external irradiation, and intracavitary irradiation. Intracavitary techniques are least utilized at the present time, in part because of the technical difficulties involved in their application and in part because of associated damage to the normal bladder wall by the large radiation doses necessary to control infiltrating tumors. Both interstitial irradiation and external supervoltage irradiation, however, are widely used. Interstitial irradiation has the theoretical advantage of placing the radiation energy directly into the tumor site and the practical disadvantages implicit in the inability to define the tumor site precisely or to distribute the radiation energy uniformly in such a site. External supervoltage irradiation has the advantage of relatively accurate and uniform dose distribution, but the disadvantage of irradiation of a relatively large volume of normal tissues. However, the protraction of treatment practically possible with external irradiation leads to acceptable levels of normal tissue damage.

Combined Treatment

Combinations of surgery and irradiation have been variously utilized in the treatment of bladder tumors since the turn of the century. Recognition of the fact that neither surgery alone nor radiation therapy alone has produced optimal results in the control of neoplastic disease has led to systematic explorations of various combinations.

A number of clinical illustrations already exist of apparent benefit to patients with bladder tumors from the use of various combinations of surgery and irradiation. (1) Improved survival from the concurrent use of radon seeds or radioactive gold grains and local excision is suggested by the reports of Barnes, Turner, and Bergman,[2] of Emmett and Winterringer,[19] and of Riches.[26] (2) Magri[19] has reported improved survival from the use of postoperative external irradiation in patients with bladder tumors treated by segmental resection. (3) Van der Werf-Messing[27] reduced the incidence of local recurrences following the suprapubic implantation of radium in bladder tumors by the utilization of postoperative external irradiation.

Preoperative irradiation has been the subject of recent discussions by Nickson and Glicksman,[23] Powers and Palmer,[25] and Cady[4, 5] and involves the systematic use of irradiation as a planned prelude to the surgical procedure. The advantages of preoperative irradiation over operative or postoperative irradiation will not be elaborated, but obviously include a tumor-host relationship undisturbed by the surgical procedure. There are three potential favorable effects from preoperative irradiation. (1) Actual destruction of tumor cells might reduce the peripheral extensions of a neoplasm and thereby make possible excision of a

previously nonresectable tumor or increase the margin of resection of an initially resectable one. (2) Reduction in the viability of tumor cells might lessen the prospects of local recurrence from tumor extensions transected at the time of surgery or from cells disseminated in the wound at the time of surgery, and might also reduce the possibility of metastasis from cells entering the hemic or lymphatic circulation during operation. (3) A favorable influence on tumor growth resulting from radiation effects on the normal host tissues or from radiation-induced alterations in "tumor immunity" has not been entirely eliminated.

Powers and Palmer point out that preoperative irradiation may be of possible benefit only if (1) the tumor cells are capable of sustaining tumor growth, (2) the tumor cells are included in the field of irradiation, and (3) the irradiation administered is capable of modifying tumor cells in a fashion which prevents local regrowth or metastasis. Preoperative irradiation cannot be expected to benefit the patient whose tumor has already extended beyond the area in which the combined treatment is to be administered, or the patient whose tumor is amenable to a high probability of control by surgery alone.

The disadvantages of preoperative irradiation include (1) preoperative uncertainty regarding the pathologic extent of the neoplasm, (2) the delay in operation necessitated by preoperative irradiation, and (3) the special hazards in convalescence from surgery imposed by the use of preoperative irradiation.

It is important to understand that what constitutes *optimal* preoperative irradiation is an unanswered question, that the answer may well vary for different tumors and for different clinical circumstances, and that questions concerning total dose, fractionation, duration, and interval between irradiation and surgery will require extended animal and clinical studies for definitive answers.

RESULTS OF TREATMENT

Treatment of Bladder Papilloma

Papilloma is a histologically benign lesion which does not infiltrate or metastasize in its natural course, but which may rarely involve the bladder wall deeply or metastasize as a consequence of iatrogenic influence. At the initial presentation about three fourths of patients with papilloma have a solitary lesion and about one fourth have multiple lesions. After destruction of the presenting tumor, about two thirds of the patients will develop other lesions. Although it is common practice to utilize the term "recurrent" in patients with bladder tumors to designate either the reappearance of an initially incompletely removed lesion at the original site or the appearance of a "new" lesion elsewhere in the bladder, these two processes should obviously be distinguished. Some 10 to 20 per cent of patients with bladder papilloma ultimately develop unmistakable histologic evidence of bladder cancer. Thus, although the 5-year life expectancy of patients with papilloma is essentially the same as that of persons of corresponding age without papilloma, the high "recurrence rate" and the possibility of development of bladder cancer

dictate the need for close follow-up. Cystoscopy is carried out at 3-month intervals until at least 3 years have elapsed from the time of the last "recurrence," and at 6-month intervals thereafter.

The treatment of papilloma is local destruction by excision or fulguration, preferably endoscopically. In patients with multiple lesions, two or rarely three separate endoscopic procedures may be necessary to destroy all visible tumors, but this approach is thought to be preferable to destruction of the tumors at a single procedure through the opened bladder. Experience at Memorial Hospital[10] with triethylene thiophosphoramide (thio-tepa) in the treatment of papilloma has paralleled that of Jones and Swinney[18] and of Veenema et al.[28] Experience with thio-tepa as a means of prophylaxis of bladder papilloma is less convincing of its effectiveness, but it is sometimes so used. Although the precise mechanism of action of thio-tepa in the instillation therapy of bladder papilloma remains uncertain, its failure as a systemic agent in the management of bladder tumors and its relative effectiveness by local instillation suggest that its action may be a locally cytotoxic one related to its diffusibility. Since diffusibility is in part dependent upon the concentration gradient and since systemic toxicity may result from the use of the conventional thio-tepa instillation, recent policy at this institution has been to utilize 15 mg. of thio-tepa in 5 to 10 ml. of diluent as the unit of instillation for the conventional treatment course. A small experience suggests that the therapeutic effects are similar to those of the larger dosages, but without risk of systemic toxicity.

Papillomatosis of the bladder, in which the entire bladder mucous membrane is replaced by a carpet of benign papillary tumors, constitutes a special but fortunately rare problem in therapy. Mucosal denudation has been suggested as a possible method of treatment.[14] Intracavitary or external irradiation, although capable of destroying such tumors in at least some patients, produces varying degrees of fibrosis of bladder muscle with associated bladder contracture, and bladder mucosal atrophy and telangiectasia with potential bleeding. It provides only limited, if any, prophylaxis against future tumor development. Accordingly, neither of these methods of radiation therapy is currently advised. Cystectomy is certainly effective in tumor control, but is a major operative procedure with associated morbidity and mortality. Papillomatosis probably constitutes the single, strongest indication for intracavitary thio-tepa treatment, since even a partial response may permit endoscopic control of the residual unresponsive lesions.

Treatment of Bladder Carcinoma

Results in the treatment of patients with various stages of bladder carcinoma by the different modalities discussed are summarized in the tables. The author has exercised no bias in choosing the material tabulated except to select series from the English literature, in which the tumors were categorized by staging, in which the methods of treatment were specified, and in which appropriate survival data were given. Differences in the methods of staging the tumors, in tumor features not encompassed by the staging categorization alone, and in treatment

Table 3. *Cancer of the Bladder—5-Year Survival Following Excision and Fulguration*

Author	Stage of Neoplasm					
	0 T.I.S.	A T.1.	B_1 T.2.	B_2 T.3.	C T.3.	D T.4.
Flocks (1951)	77% (130/168)		47% (68/142)			
Milner* (1954)		70% (of 57)	57% (of 89)	23% (of 86)	7% (1/13)	
Nichols & Marshall (1956)	81% (70/86)		15% (3/20)			
Barnes (1967)	63% (146/233)**		40% (46/114)		5% (3/57)	

* Not all cases had been followed 5 years.
** Papilloma included

mortality create additional uncertainties regarding the precise comparability of the data.

SURGICAL TREATMENT. In Table 3 are tabulated 5-year survival rates following excision and fulguration of bladder tumors.[1, 11, 22, 24] For the most part transurethral procedures were employed, although some patients had suprapubic excision and fulguration. In Table 4 are shown the 5-year survival rates following the treatment of bladder cancer by segmental resection.[11, 16, 19, 20, 26] Table 5 gives 5-year survival rates for patients with bladder cancer treated by simple total cystectomy.[3, 6, 7, 16, 26] With the surgical specimens from segmental resection or cystectomy it is possible accurately to stage the neoplasm pathologically with regard to degree of infiltration of the bladder wall, although, of course, the presence or absence of regional lymph node metastasis cannot be based upon evaluation of such specimens. Pathologic staging is obviously less accu-

Table 4. *Cancer of the Bladder—5-Year Survival Following Segmental Resection*

Author	Stage of Neoplasm					
	0 T.I.S.	A T.1.	B_1 T.2.	B_2 T.3.	C T.3.	D T.4.
Flocks (1951)			38% (5/13)			
Marshall, Holden and Ma (1956)	62.5% (40/64)			22% (11/50)		
Jewett (1957)	70.0% (16/23)			8% (4/48)		
Riches (1960)	58% (7/12)		36% (16/44)		0 (0/6)	
Magri (1962)	80% (8/10)		38% (10/26)		26% (5/19)	

Table 5. *Cancer of the Bladder—5-Year Survival Following Simple Total Cystectomy*

Author	Stage of Neoplasm					
	0	A	B_1	B_2	C	D
Colby & Kerr (1951)	16% (2/12)		8% (2/25)			
Brice, Marshall, Green & Whitmore (1956)	37% (25/68)			9% (8/88)		4% (1/24)
Cordonnier (1956)*	37%		37%		25%	
Jewett (1957)	50% (5/10)			9% (4/44)		
Riches (1960)	42% (15/36)		9% (3/33)		4% (1/28)	

* Total of 48 patients

rate in patients who have had local excision and fulguration as the method of treatment, even when one exercises special care to assure the best possible pathologic examination of the surgical specimens. In Table 6 are tabulated the survival results in 230 patients who had radical surgery for bladder cancer.[29] Sixty-seven patients had pelvic exenteration and 163 had radical cystectomy, but since a preliminary analysis disclosed no important differences in the ability of either procedure to control the cancer, the two series were combined in this tabulation.

Disregarding the hazards of comparing survival data in patients with lesions characterized by so many recognized variables according to the two selected criteria of method of treatment and pathologic stage, Table

Table 6. *Cancer of the Bladder—5-Year Survival Following Radical Surgery*

CANCER OF THE BLADDER 5 Year Survival Following Radical Surgery						
Author	Stage of Neoplasm					
	0	A	B_1	B_2	C	D
Whitmore & Marshall (1961)	47% (35/75)			17% (4/23)	13% (7/53)	3% (2/74)

7 summarizes the range of survival rates reported for the various methods of surgical treatment of the various stages of bladder cancer. One must bear in mind that there is a progressive improvement in the accuracy of staging as the method of surgical treatment becomes more radical, and that this fact creates a bias which potentially favors the more radical methods in the end results. Several facts are evident from an inspection of these data:

(1) For each method of surgical treatment, survival results are better with low-stage than with high-stage tumors, and for each method of treatment, results are poor with tumors of metastatic stages.

(2) The best results in the treatment of low-stage tumors are ostensibly with conservative treatment, presumably as a consequence of two considerations: (a) operative mortality and morbidity are appreciably greater with radical surgery than with more conservative methods of treatment; and (b) the case selection implied: patients who undergo cystectomy for low-stage tumors are generally those in whom the tumors are unsuitable for conservative surgery because of multiplicity, or because of repeated recurrences, or because or rapidity of recurrences, or because the tumors are of high grade.

(3) With regard to high-stage tumors the similarity of survival rates with different methods of surgical treatment is also to some extent an artifact of case selection. Deeply infiltrating bladder cancers of a size and at a site susceptible to control by transurethral resection are rare. Furthermore, segmental resection is ideally applicable only to a highly selected group of patients. The essentially similar results after either segmental resection or radical surgery for the treatment of high-stage bladder cancers are not really surprising. Part of this similarity may be a consequence of the possibility that whatever advantage radical surgery may have over segmental resection in control of the bladder cancer per se is lost by the greater operative mortality of the latter procedure. Some apparent survival advantage may be gained in patients with high-stage tumors treated by radical surgery due to the clinical and pathologic opportunities thereby offered for distinguishing between high-stage and

Table 7. *Cancer of the Bladder—5-Year Survival Following Different Methods of Surgical Treatment*

Treatment:	Stage of Neoplasm					
	0	A	B_1	B_2	C	D
Excision & fulguration	70 - 81 %		47 - 57 %	up to 23 %	up to 7 %	
Segmental resection	62.5 - 70 %			8 - 22 %		
Simple total cystectomy	37.0 - 50 %			9 %		4 %
Radical surgery	47.0 %			17 %	13 %	3 %

Table 8. *Five-Year Survival After Radical Surgery of Patients with Stage D Bladder Cancer*

Total patients 74

Postoperative deaths 11 (15%)

Stage	Number	5 yr. Survivors
D_1	55	2 (4%)
D_2	19	0
With only 1 or 2 nodes invaded	13	2 (16%)
With prostatic invasion	20	0
With invasion of other adjacent organs	10	0
D (Total)	74	2 (3%)

metastatic-stage lesions, a distinction that is less likely to be made in patients treated by segmental resection or simple total cystectomy. That segmental resection, in properly selected cases, seems to control as many cancers as does radical surgery may be in part a consequence of the fact that radical surgery is essentially an extended segmental resection to which a lymph node dissection, which only rarely controls metastatic disease, is added. The similarity of results in treatment of high or metastatic stages of bladder cancer by simple versus radical cystectomy is also expected and is a reflection of the fact that the prospects of surgical control of a bladder cancer, once it has extended through the bladder wall or has metastasized, are small.

In Table 8 is given the survival experience in patients with stage D lesions subjected to radical surgery. Although the over-all survival rate is small, the selected experience in which metastases had not extended beyond the obturator area on one side or the other resulted in two 5-year survivors among 13 patients, thus justifying continued utilization of limited lymph node dissection. Indeed, the survival rate achieved in this highly selected group of patients with limited lymph node metastasis is of the same order as that achieved in patients with stage B_2 and C lesions without metastasis. Disregarding the small numbers of patients involved in the series, one may argue that, if the survival rate obtained in patients with limited lymph node metastases does not justify the surgical effort, then radical surgery is hardly justified for patients with stage B_2 or C lesions either. The similarity of the 5-year survival rates following radical cystectomy for patients with stage B_2 or C lesions and for patients with limited lymph node metastasis may also be interpreted as consistent with the possibility that occult lymph node metastases are present in a substantially greater proportion of patients with stage B_2 or C lesions than is commonly suspected by the clinician or detected by the pathologist. The 5-year survival of patients following the radical surgical treatment of bladder tumors which have invaded adjacent organs has been nil in this small experience.

Table 9. *Cancer of the Bladder—5-Year Survival After Interstitial Radiation*

Author	Stage of Neoplasm					
	0 T.I.S.	A T.1.	B_1 T.2.	B_2 T.3.	C T.3.	D T.4.
Poole-Wilson (1954) (Radon)		54% (6/11)	39% (7/18)		7% (1/15)	
Bloom (1960) (Tantalum)		70% (31/44)	40% (12/30)			
Van Der Werf Messing (1964) (Radium)		64% (of 23)	34% (of 82)		10% (of 43)	
Munro (1964) (Gold)		70% (19/27)	39% (7/18)		0% (0/13)	

Table 10. *Cancer of the Bladder—5-Year Survival After External Radiation*

Author	Stage of Neoplasm					
	0 T.I.S.	A T.1.	B_1 T.2.	B_2 T.3.	C T.3.	D T.4.
Friedman (1959)				16%		
Wallace (1959)		24% (of 21)	11% (of 37)		11% (of 47)	
Dick (1962)		73% (of 15)	46% (of 28)		0% (of 11)	
Brady and Gislason (1963)		100% (4/4)		22% (2/9)		0% (0/16)
Collins (1964)		33% (2/6)	23% (3/13)	(0/2)		
Sagerman et al (1965)			33% (25/76)		25% (of 46)	
Kurohara et al (1965)		32% (of 41)		13% (of 62)		
Crigler et al (1966)		32% (of 31)		28% (of 46)		6% (of 49)

REFERENCES FOR TABLES 9 AND 10

Bloom, H. J. G.: Treatment of carcinoma of the bladder, A symposium. Radiology, 33:471-479 (Aug.), 1960.

Brady, L. W., and Gislason, G. J.: The management of carcinoma of the bladder using supervoltage modalities. Amer. J. Roentgenol., 89:150-154 (Jan.), 1963.

Collins, C. D.: Influence of previous surgery on results of megavoltage radiotherapy in carcinoma of bladder. Lancet, 2:988-990 (Nov. 7), 1964.

Crigler, C. M., Miller, L. S., Guinn, G. A., and Schillaci, H. G.: Radiotherapy for carcinoma of the bladder. J. Urol., 96:55-61 (July), 1966.

Dick, D. A. L.: Carcinoma of the bladder treated by external irradiation. Brit. J. Urol., 34:340-350 (Sept.), 1962.

Friedman, M.: Supervoltage (2-Mvp) rotation irradiation of cancer of the bladder. Radiology, 73:191-208 (Aug.), 1959.

Kurohara, S. S., Rubin, P., and Silon, N.: Analysis in depth of bladder cancer treated by supervoltage therapy. Amer. J. Roentgenol., 95:458-467 (Oct.), 1965.

Munro, A. I.: The results of using radioactive gold grains in the treatment of bladder growths. Brit. J. Urol., 36:541-548 (Dec.), 1964.

Poole-Wilson, D. S.: The treatment of malignant tumors of the bladder by irradiation therapy. Brit. J. Urol., 26:326-342 (Dec.), 1954.

Sagerman, R. H., Bagshaw, M. A., and Kaplan, H. S.: Linear accelerator supervoltage radiation therapy: Carcinoma of the bladder. Amer. J. Roentgenol., 93:122-127 (Jan.), 1965.

Van Der Werf-Messing, B.: Treatment of carcinoma of the bladder with radium. Clin. Radiol., 15:16-25 (Jan.), 1964.

Wallace, D. M.: Tumors of the Bladder. Edinburgh and London, E. & S. Livingstone Ltd., 1959, pp. 312-313.

Table 11. *Cancer of the Bladder—5-Year Survival After Radiation*

Treatment	Stage of Neoplasm					
	0 T.I.S.	A T.1.	B_1 T.2.	B_2 T.3.	C T.3.	D T.4.
External	24% - 73%		11% - 46%		0% - 25%	0% - 6%
Interstitial		54% - 70%	34% - 40%		7% - 10%	

RADIATION TREATMENT. In Tables 9 and 10, respectively, are indicated some results of various forms of interstitial irradiation and supervoltage irradiation in the treatment of various stages of bladder cancer. In Table 11 the ranges of survival rates for patients with different stages of bladder cancer treated by either interstitial or external irradiation are combined. One notes that the prospects of survival with any method of radiation therapy become progressively less as the stage of the neoplasm increases, that there is a relatively wide range of survival rates reported for similar methods of treatment of tumors of similar stage, and that the range of survival rates for tumors of similar stage treated by the different methods is similar.

In Table 12 are summarized the ranges of survival rates following treatment by either irradiation or surgery of tumors of comparable stage. Without debating the comparability of the patients in the two treatment groups, the basic similarity of the survival experiences is impressive and inescapable. One may conclude that: (1) the primary determinant of survival in the patient with bladder cancer is not the method of treatment but the nature of the tumor (characterized in this analysis by tumor stage). (2) The similarity of the survival experiences with tumors of

Table 12. *Cancer of the Bladder—5-Year Survival After All Types of Treatment*

Treatment	Stage of Neoplasm					
	0 T.I.S.	A T.1.	B_1 T.2.	B_2 T.3.	C T.3.	D T.4.
Radiation	24% - 73%		11% - 46%		0 - 25%	0 - 6%
Surgery	37% - 81%		9% - 47%		0 - 26%	0 - 4%

Table 13. *Cancer of the Bladder—Operative Morbidity and Mortality*

	Cystectomy only	Preoperative radiation and cystectomy
Deaths	16/145 (11%)	14/121 (12%)
Complications	62/145 (43%)	52/121 (43%)

similar stage treated by different methods implies that each treatment has the same or similar weaknesses, or that different methods have different weaknesses that yield similar results, or both. (3) Tumors which fail to be controlled by one method of treatment may conceivably be controlled by other methods. (4) Results with the surgical or radiation therapy of bladder cancer leave much to be desired.

COMBINED TREATMENT. Since 1959, preoperative irradiation combined with radical cystectomy has been employed in a selected group of patients with bladder tumors at Memorial Hospital.[30] Patients were generally selected for cystectomy for: (1) low-stage carcinomas, either initially too extensive for conservative treatment, or rapidly recurrent after conservative treatment, or repeatedly recurrent following conservative treatment, especially if the lesions were of high grade, either initially or subsequently; or (2) high-stage carcinomas, not suitable for segmental resection because of prior tumor elsewhere in the bladder, or because of multiplicity, or because of proximity to the bladder neck.

Preoperative irradiation was planned for all patients in whom cystectomy was recommended, except those who were referred for cystectomy after failure of irradiation to control the tumor. The plan was to administer 4000 rads to the bladder and true pelvis using supervoltage irradiation in a period of 4 weeks. Patients were explored in anticipation of performing cystectomy between 1 and 3 months after the completion of radiation therapy. A review of experience with reference to operative mortality and morbidity (Table 13), effects of radiation therapy on the tumor (Table 14) and survival (Tables 15 to 18) is presented. In an attempt to place the results of this combined treatment program in perspective, a series of patients who had only radical cystectomy for bladder cancer is offered for comparison. The latter series of 145 patients is derived from an experience of 230 patients subjected to radical surgery for bladder cancer in which those who had either prior radiation therapy or pelvic exenteration or both were excluded. Although the validity of the comparisons may be questioned, since the two groups were not the result of a controlled study and were not accumulated contemporaneously, the methods and accuracy of clinical staging, the criteria for selection of patients for radical cystectomy, and the technique of radical cystectomy were essentially the same in the two series. In the tabulations, the patients having radical cystectomy only are referred to as the "old series" while those having preoperative irradiation and cystectomy are referred to as "protocol RT."

Table 14. *Cancer of the Bladder—Comparison of Preradiation Clinical Stage to Postsurgical Pathologic Stage*

CLINICAL STAGE		PATHOLOGIC STAGE				
		No tumor	In situ	A, B_1	B_2C	D
OAB_1	44	6	10	17	4	7
B_2C	79	9	1	15	21	33
D	15			1	5	9
Total	138	15	11	33	30	49

Between 1959 and 1966, 327 cystectomies were advised for the previously cited indications in patients with bladder cancer. In 32 patients preoperative irradiation was not employed, and in 118 patients prior radiation therapy was employed but not according to the prescribed protocol. These 150 patients are excluded from the present analysis. In the remaining 177 patients, protocol radiation therapy, followed by radical cystectomy, was planned. Thirty-nine patients had protocol irradiation but did not have subsequent laparotomy or cystectomy, primarily because subjective and objective improvement following the radiation therapy was sufficient to result in the patient's refusal or, less commonly, the surgeon's reluctance, to proceed with radical cystectomy. In 17 patients, laparotomy revealed nonresectable neoplasm. Thus, 121 patients actually had radical cystectomy following protocol irradiation.

The operative mortality and morbidity following radical cystectomy were not appreciably altered by preoperative irradiation (Table 13). The specific causes of operative mortality in the two series were similar. Vesical space infections were the single most common complication in both series, but the duration of morbidity was greater in the patients who had had radiation therapy.

A comparison of the preradiation clinical stage of the tumor and the postradiation postsurgical pathologic stage (Table 14) provides information about the effects of irradiation on the tumor. The tabulation includes 121 patients on whom cystectomy was actually accomplished and 17 patients in whom laparotomy revealed nonresectable tumor. Since, in all but two instances, pretreatment biopsies had revealed tumor beyond the in situ stage and since no effort was made to eradicate tumor by transurethral measures prior to radiation therapy, it is probable that in 24 of the 138 patients, a reduction in tumor stage occurred as a consequence of the irradiation. Multiple blocks were examined from the bladders of these patients, but step or serial sections were not routinely employed.

Of the 11 patients with in situ cancer only in the cystectomy specimen, two have died of bladder cancer and one of unrelated cause. Of the surviving eight patients, six have survived for more than 2 years, in-

Table 15. *Cancer of the Bladder—Survival of Patients Having Protocol Radiation Only*

Clinical Stage	2 years	3 years	4 years	5 years
OAB_1 (17)	11/16 (83%)	8/15 (53%)	3/8 (38%)	1/5 (20%)
B_2C (18)	8/16 (50%)	5/15 (33%)	1/13 (8%)	1/8 (12%)
D (4)	1/3	1/2	1/2	

cluding two for 3 years, one for 4 years, and one for more than 5 years.

Among the 39 patients who had protocol irradiation without subsequent laparotomy (Table 15), there were 11 whose biopsies and urinary cytologic studies became negative following irradiation, and five have died, three from cardiovascular causes and two from cancer. Of the remaining six patients, one is living less than 2 years, one for 2 years, three for 3 years, and one for 5 years since the irradiation.

In Table 16 survival rates of patients with pathologically low-stage lesions from each of the two series are calculated at 2, 3, 4, and 5 years on the basis of the number of survivors relative to the total number at risk for the respective follow-up intervals. The 2, 3, 4, and 5-year survival rates in the two series are similar.

A similar tabulation (Table 17) is given for patients in the two series with pathologically high-stage neoplasms. The survival rates at 2, 3, 4, and 5 years are all better in those patients having protocol irradiation than in the purely surgical series.

For patients with pathologically stage D lesions (Table 18) the prognosis is very poor and has not been favorably altered by preoperative irradiation.

Although the number of patients involved in these pilot studies is small and although the validity of comparisons between the protocol group and the purely surgical group may be questioned, some tentative observations relative to this experience are permissible:

(1) No major impact on operative mortality or morbidity resulted from preoperative irradiation. (2) The apparent destruction of tumor in slightly more than 10 per cent of the cases treated and the reduction in

Table 16. *Cancer of the Bladder—Survival Rates of Patients with Tumors of Pathologic Stages O, A, and B_1*

	2 years	3 years	4 years	5 years
Old Series (51)	37/51 (73%)	33/51 (65%)	29/51 (65%)	28/51 (55%)
Protocol Series (59)	45/58 (77%)	33/49 (67%)	24/40 (60%)	15/29 (51%)

Table 17. *Cancer of the Bladder—Survival Rates of Patients with Tumors of Pathologic Stages B_2 and C*

	2 years	3 years	4 years	5 years
Old Series (60)	17/60 (28%)	12/60 (20%)	11/60 (18%)	10/60 (17%)
Protocol Series (30)	14/29 (48%)	11/27 (40%)	8/23 (34%)	6/16 (37%)

tumor stage in an additional 6 to 7 per cent is evidence of a definite antitumor effect from the preoperative irradiation. (3) The radiosensitivity of some bladder tumors is emphasized by the occasional long-term survival following 4000 rads in 4 weeks among the 39 patients who had protocol irradiation only. Although the information regarding the radioresponsiveness of bladder tumors derived from this study is incomplete, it clearly demonstrates that some bladder tumors are relatively radiosensitive and a very few are apparently radiocurable with the radiation program utilized. (4) A comparison of survival data for patients with low-stage tumors treated on the one hand by radical cystectomy and on the other hand by preoperative irradiation plus radical cystectomy reveals no significant differences. This suggests that control of the tumor in the area of the operation (and irradiation) is either not the basis for the therapeutic failure or has not been aided by the irradiation. On the other hand, the apparent improvement in survival in patients with high-stage tumors receiving preoperative irradiation is consistent with the possibility that the circumstances of treatment failure following surgery alone are favorably altered by the addition of preoperative irradiation. In the case of metastatic stage tumors, the failure to demonstrate improvement in survival from the use of preoperative irradiation suggests that the causes of treatment failure following surgery alone are outside the radiation portals. Nickson and Glicksman have pointed out that "... the optimal situation for combined treatment to be effective is for the patient with neither a very high nor very low probability of survival. In the former instance it is not necessary, in the latter it is insufficient."

Assuming that this experience does indeed represent a favorable effect from the use of preoperative irradiation, how can or should the program be modified to improve the results, or even maintain the same results with a more practical program of therapy? Although extended

Table 18. *Cancer of the Bladder—Survival Rates of Patients with Tumors of Pathologic Stage D*

	2 years	3 years	4 years	5 years
Old Series (34)	9/34 (26%)	5/34 (15%)	3/34 (9%)	2/34 (6%)
Protocol Series (32)	4/26 (15%)	1/18 (6%)	0/15	0/13

animal and clinical studies will be necessary to answer this and similar questions, a modification of the above protocol has been under exploration for the past 2 years in which 2000 rads of preoperative supervoltage irradiation is administered to the bladder and true pelvis in five treatments in not more than 10 days over-all time and followed within 2 weeks by radical cystectomy.

REASONS FOR POOR RESULTS

If one defines a poor result as a mortality following treatment, it is apparent that death may be the consequence of three general causes: (1) Death from natural causes as reflected in life expectancy data. This is a reflection of the mortal nature of man, and not of the inadequacy of bladder tumor therapy. (2) Death as a direct or indirect consequence of the treatment. This includes treatment mortality and, for example, death from upper urinary tract obstruction and infection as a consequence of urinary diversion. Although efforts should be made to reduce or eliminate such mortality, such calculated risks should not, per se, be regarded as contraindications to treatment, but rather as reminders that the risk of justifiable treatment should be less than the risk of the disease treated.

(3) Death due to the cancer. Death as a consequence of the cancer is clearly a reflection of the inadequacy of the treatment (or treater) and includes the following poorly quantified possibilities which apply in varying degrees both to surgical and to radiation therapy:

(a) Cancer beyond the limits of the treatment applied. This includes the entire range of possibilities, from the well-localized tumor which is simply inadequately treated to the tumor which has already extended beyond the limits of the most extensive therapeutic effort. Intelligent application of current knowledge of the relationship between tumor stage and theoretical curability has increased understanding of this cause of treatment failure. It has been suggested by Franksson[12] that the tumor which is limited to the mucosa is theoretically 100 per cent curable, but that the tumor which has penetrated into or beyond the submucous layer is associated with a prognosis which becomes worse the greater the degree of penetration. The data of Jewett and Strong relating the theoretical curability of a tumor by cystectomy to its pathologic extent illustrate this relationship. Finally, the treatment experience cited supports this concept.

(b) Cancer recurrence or metastasis as a consequence of treatment. Although the iatrogenic dissemination of cancer as a consequence of surgical maneuver, either by wound implantation or through hemic or lymphatic spread, undoubtedly occurs, its precise contribution to treatment failure is undetermined. Wound implants have been reported in up to 20 per cent of patients after suprapubic operations,[21] and the precise frequency after cystectomy is undetermined. Recurrences in the bladder neck area and urethra after transurethral treatment of tumors elsewhere in the bladder suggest that such recurrences may be at least in part the consequence of instrumental trauma.[15] The influence of prior transurethral resection of the bladder wall on the behavior of any future

tumors occurring at that particular site in the bladder wall is undetermined. The occurrence of tumors at sites of stricture in the urethra, or in the prostatic fossa after enucleation or transurethral prostatectomy performed at the time of treatment of bladder tumors, suggests the possibility of direct tumor implantation at traumatized sites. One need not presume that the operation was poorly selected for the particular tumor in order to invoke such explanations of therapeutic failure, since the local bladder tumor process may have been controlled by the very procedure that contributed to the development of the tumor elsewhere; yet such occurrences obviously constitute limitations of the respective methods of treatment.

(c) "New" cancers. Reference has already been made to the inadequacy of the term "recurrences"—a term which does not distinguish between the cancer which is the sequel to the initially inadequately treated lesion and the truly "new" growth. Deaths due to "new" cancers may be considered as part of the natural history of the disease, whereas those due to strict "recurrences" represent failures alluded to under (a) above. Whether the "new" cancers which develop at traumatized sites in the bladder or urethra are the consequence of "seeding" or of "new" cancers developing in a mucous membrane made more susceptible to the tumorigenic stimulus as a consequence of trauma remains uncertain, but no attempt need be made at present to distinguish these possibilities. The possibilities of "new" growths include:

(1) Bladder "new growths." The incidence of vesical "new growths" varies from 25 to more than 50 per cent following the transurethral resection of papilloma and various papillary carcinomas and is approximately 25 per cent after segmental resection. The implication of such observations is that, even if the patient is cured of the tumor with which he presents, he experiences a continuing risk from the possibility of new lesions in the bladder. This risk constitutes one of the theoretical advantages of cystectomy over more conservative measures as a means of treatment of bladder cancer.

(2) Urethral "new growths." Cordonnier and Spjut[8] reported a 4 per cent clinical incidence of urethral cancer following cystectomy for bladder cancer, and Gowing[13] found a 20 per cent incidence of in situ carcinoma in the urethras of men examined at autopsy following cystectomy for bladder cancer.

(3) Ureteral "new growths." That patients with bladder cancer have a high incidence of ureteral cancer is suggested by the observation in Memorial Hospital experience that approximately 10 per cent of patients subjected to cystectomy for cancer of the bladder will have incidental in situ carcinoma in one or both ureters.

(4) Renal pelvis tumors. Patients with bladder cancer are at risk of developing renal pelvis tumors, although the precise incidence is undefined.

All of these possibilities require the type of quantitation that will permit, for the individual patient, not only an evaluation of the prospects of successfully treating the tumor with which he presents, but also an estimate of the future risks of the disease.

CURRENT TREATMENT PROGRAM

The program of therapy currently employed at Memorial Hospital may be summarized as follows:

(1) Papilloma. The treatment is local destruction of the tumor by transurethral resection or fulguration or both. Cystoscopy is performed at 3-month intervals until the patient has been disease-free for at least 3 years and at 6-month intervals thereafter. Thio-tepa instillation is employed prophylactically when interval cystoscopies suggest a pattern of increasing tumors. Therapeutic thio-tepa instillation is employed in selected patients in an attempt to reduce the number or size of multiple tumors.

(2) Low-stage, low-grade carcinoma. Transurethral excision and fulguration remains the treatment of choice, with cystoscopic follow-up examination at 3-month intervals for at least 5 years. Some patients with low-grade, low-stage tumors are subjected to cystectomy by reason of the multiplicity of the lesions, or the rapid "recurrence" of the lesions, or the multiplicity of "recurrences" of the lesions, but the optimal time for cystectomy in such circumstances is by no means clear.

(3) Low-stage, high-grade carcinoma. The therapeutic decision rests between segmental resection and preoperative irradiation, followed by radical cystectomy (vide infra).

(4) High-stage carcinoma, whether high-grade or low-grade, is treated either by segmental resection or by preoperative irradiation combined with radical cystectomy. Segmental resection is employed in the patient in whom the lesion is solitary, in whom there is no history of antecedent tumor elsewhere in the bladder, and in whom the tumor is so localized as to permit resection with a minimum of 2 cm. of healthy bladder wall at all points peripheral to the base of the tumor. Radical cystectomy is otherwise employed.

(5) Metastatic-stage carcinoma. Although the survival prospects of patients with stage D_1 tumors are small, a few long-term survivals have resulted from radical surgery. Accordingly, preoperative irradiation followed by radical cystectomy remains under exploration. For patients with stage D_1 lesions judged not suitable for such treatment and for patients with stage D_2 lesions, the treatment is designedly palliative and includes various combinations of irradiation, chemotherapy, and surgery, depending upon the precise circumstances.

CONCLUSION

Bladder tumor may represent only one presentation of a neoplasia to which the entire urothelium is variously susceptible. Against the background of such a possibility, the limitations of current therapeutic methods are obvious. Although future hope for the control of bladder tumors includes the possibility of identifying and eliminating exogenous or endogenous cause(s) of the disease, the need for efforts to improve current therapy of the disease remains.

REFERENCES

1. Barnes, R. W.: Endoscopic surgical treatment of bladder tumors. Urol. Digest, 6:13-15 (Jan.), 1967.
2. Barnes, R. W., Turner, C. L., and Bergman, R. T.: Treatment of bladder tumors. Calif. Med., 65:95-98 (Sept.), 1946.
3. Brice, M., II, Marshall, V. F., Green, J. L., and Whitmore, W. F.: Simple total cystectomy for carcinoma of the urinary bladder: 156 cases five years later. Cancer, 9:576-584 (May-June), 1956.
4. Cady, B.: Preoperative radiation. Surg., Gynec., Obstet., *126*:851-865 (April), 1968.
5. Cady, B.: Preoperative radiation. Surg., Gynec., Obstet., *126*:1091-1105 (May), 1968.
6. Colby, F. H., and Kerr, W. S., Jr.: Carcinoma of the bladder. An evaluation of total cystectomy and other methods of treatment. New Eng. J. Med., 244:504-506 (April), 1951.
7. Cordonnier, J. J.: Value of cystectomy in management of carcinoma of bladder. Trans. Amer. Assoc. Genito-Urinary Surgeons, 48:107-111, 1956.
8. Cordonnier, J. J., and Spjut, H. J.: Urethral occurrence of bladder carcinoma following cystectomy. Trans. Amer. Assoc. Genito-Urinary Surgeons, 53:13-18, 1961.
9. Emmett, J. L., and Winterringer, J. R.: Experience with implantation of radon seeds for bladder tumors: Comparison of results with other forms of treatment. J. Urol., 73: 502-515 (March), 1955.
10. Esquivel, E. L., Jr., Mackenzie, R. A., and Whitmore, W. F., Jr.: Treatment of bladder tumors by instillation of thio-tepa, actinomycin D, or 5-fluorouracil. Invest. Urol., 2:381-386 (Jan), 1965.
11. Flocks, R. H.: Treatment of patients with carcinoma of the bladder. J.A.M.A., *145*:295-301 (Feb. 3), 1951.
12. Franksson, C.: Tumours of the urinary bladder. Acta Chir. Scandinav., Suppl. 151, 1950.
13. Gowing, N.F.C.: Urethral carcinoma associated with cancer of the bladder. Brit. J. Urol., 32:428-439 (Dec.), 1960.
14. Harada, N., and Kusunoki, T.: Results of the mucosal denudation for bladder tumors: An interim report. J. Urol., *99*:725-727 (June), 1968.
15. Hinman, F., Jr.: The recurrence of bladder tumors. J. Urol., *83*:294-300 (March), 1960.
16. Jewett, H. J.: The diagnosis and treatment of carcinoma of the bladder. Pennsylvania Med. J., 60:473-477 (April), 1957.
17. Jewett, H. J., and Strong, G. H.: Infiltrating carcinoma of the bladder: Relation of depth of penetration of the bladder wall to incidence of local extension and metastases. J. Urol., 55:366-372 (April), 1946.
18. Jones, H. C., and Swinney, J.: Thio-tepa in the treatment of tumors of the bladder. Lancet, 2:615-618 (Sept. 16), 1961.
19. Magri, J.: Partial cystectomy: A review of 104 cases. Brit. J. Urol., *34*:74-87 (March), 1962.
20. Marshall, V. F., Holden, J., and Ma, K. T.: Survival of patients with bladder carcinoma treated by simple segmental resection. Cancer, 9:26-29 (May-June), 1956.
21. Melicow, M. M.: Tumors of the urinary bladder: A clinicopathological analysis of over 2500 specimens and biopsies. J. Urol., 74:498-521 (Oct.), 1965.
22. Milner, W. A.: The role of conservative surgery in the treatment of bladder tumors. Brit. J. Urol., 26:375-384 (Dec.), 1954.
23. Nickson, J. J., and Glicksman, A. S.: Preoperative radiotherapy in cancer. J.A.M.A., *195*: 138-142 (March 14), 1966.
24. Nichols, J. A., and Marshall, V. F.: Treatment of histologically benign papilloma of the urinary bladder by local excision and fulguration. Cancer, 9:24-25 (May-June), 1956.
25. Powers, W. E., and Palmer, L. A.: Biologic basis of preoperative radiation treatment. Amer. J. Roentgenol., *102*:176-192 (Jan.), 1968.
26. Riches, E.: Choice of treatment in carcinoma of the bladder. J. Urol., *84*:472-480 (Sept.), 1960.
27. Van Der Werf-Messing, B.: Treatment of carcinoma of the bladder with radium. Clin. Radiol., *15*:16-25 (Jan.), 1964.
28. Veenema, R. J., Dean, A. L., Roberts, M., Fingerhut, B., Chowdhury, B. K., and Tarassoly, H.: Bladder carcinoma treated by direct instillation of thio-tepa. J. Urol., *88*:60, 1962.
29. Whitmore, W. F., Jr., and Marshall, V. F.: Radical total cystectomy for cancer of the bladder: 230 consecutive cases five years later. J. Urol., *87*:853-868 (June), 1962.
30. Whitmore, W. F., Jr., Grabstald, H., Mackenzie, R. A., Iswariah, J., and Phillips, R.: Preoperative irradiation with cystectomy in the management of bladder cancer. Amer. J. Roentgenol., *102*:570-576 (March), 1968.

Chemotherapy and Surgery in the Treatment of Gestational Trophoblastic Neoplasms

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The effectiveness of chemotherapy in curing women with metastases from choriocarcinoma or hydatidiform mole has been an exciting development in the field of oncology. In the relatively short span of 12 years since the earliest report of this success,[17] chemotherapy has also been demonstrated to be even more effective in treating non-metastatic trophoblastic disease.[5, 10] This has led to an evaluation of the respective roles of surgery and chemotherapy in the treatment of women with these diseases.

The purpose of this paper is to present one approach to the treatment of these patients with particular emphasis on the simultaneous use of both surgery and chemotherapy; that is, surgery carried out during a course of adjunctive chemotherapy. In order to put this in proper perspective, a description of the classifications of gestational trophoblastic diseases will first be given. Following this will be a brief resume of the reported effectiveness of chemotherapy and surgery alone, our rationale for the use of adjunctive chemotherapy with surgery, and an outline of our current approach to specific clinical conditions. Finally, a brief description will be given of the unusual ways in which metastatic choriocarcinoma can become manifest, so that surgical specialists other than gynecologists can anticipate rather than be surprised by the diagnosis of metastatic trophoblastic disease.

CLASSIFICATION

Gestational trophoblastic neoplasms are usually classified according to histology and location. The pathologic diagnosis of hydatidiform mole[9]

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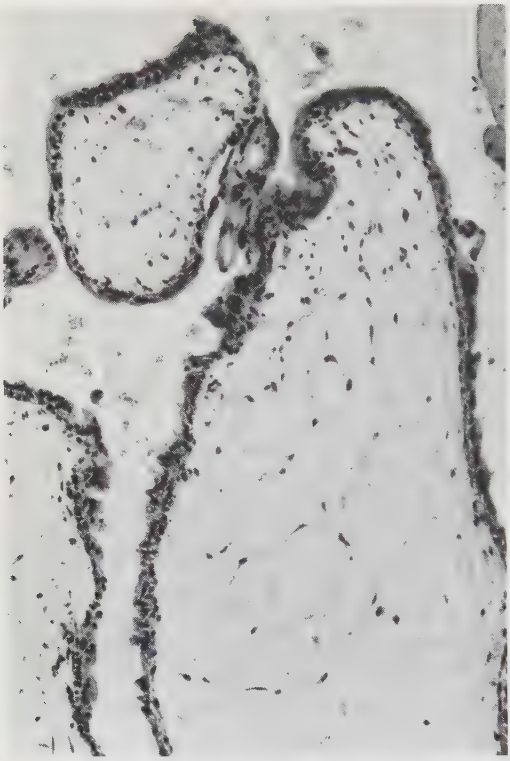

Figure 1. Hydatidiform mole (hematoxylin and eosin stain, ×138). This benign-appearing tumor shows edematous villi, absence of fetal vessels, and minimal proliferation of the trophoblastic cells covering the villi. This patient subsequently developed pulmonary metastases which responded to chemotherapy.

is made on the basis of swollen chorionic villi, absence of fetal vessels, varying degrees of trophoblastic proliferation, and marked hemorrhage and necrosis, as shown in Figure 1. Although these tumors are generally considered benign, they can undergo malignant change. They usually occur as a pregnancy in which the fetus has died early and thus are not associated with a term pregnancy except in the rare situation of coexistence of a molar and normal gestation in a twin pregnancy. The malignant trophoblastic tumor, choriocarcinoma, is composed of sheets of malignant trophoblastic tissue unaccompanied by villi, as shown in Figure 2. It is also associated with extensive tissue necrosis and hemorrhage and can accompany any type of pregnancy. About one fourth follow full-term delivery of a normal infant, an equal number follow early abortion which had no molar change, and the largest number follow molar pregnancy.[9] These growths can also be characterized by their location: limited to the endometrial cavity, locally invasive or metastatic.

The possibility of progression from benign to malignant tissue in a given case, the difficulty of determining histology in metastatic deposits without exploration, and the evidence that all forms of metastatic disease respond to chemotherapy have each given impetus to the adoption of a simpler classification. The term "gestational trophoblastic disease," divided only into metastatic or nonmetastatic, has recently been pro-

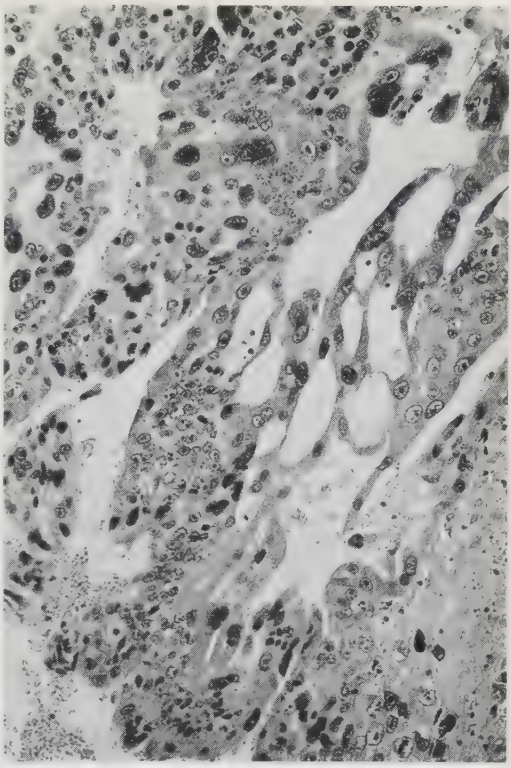

Figure 2. Choriocarcinoma (hematoxylin and eosin stain, ×138). The tumor is composed of both syncytiotrophoblastic and cytotrophoblastic cells. Numerous mitotic figures, as well as hemorrhage and necrosis, are typical. This tumor was diagnosed by dilatation and curettage 8 weeks following a full-term delivery.

posed.[11] Essential to this diagnosis is evidence for the excretion of human chorionic gonadotropin (HCG).

The measurement of HCG in these patients is critical in their diagnosis, management, and follow-up. Although these tumors usually produce huge quantities of HCG, there are many exceptions to this. The use of routine pregnancy tests, which can be quantitated by testing dilutions of urine, is adequate when the HCG excretion is high. The problem arises in following a woman's HCG level until it drops to the level of normal urinary pituitary gonadotropin excretion, a much smaller amount than is measured in a pregnancy test. In Ross's report of patients with nonmetastatic trophoblastic disease[20] (either choriocarcinoma or persistent mole), one-fourth of the patients had a level less than the sensitivity of a routine pregnancy test but clearly above the level of pituitary gonadotropins. A labotatory which has facilities to concentrate urine and measure these low levels of gonadotropin is necessary for the successful treatment of these patients.

RESULTS OF CHEMOTHERAPY

Metastatic Trophoblastic Disease

The first encouraging report of complete remission of metastatic gestational trophoblastic diseases following chemotherapy[17] has been

followed by many similar reports.[5, 12, 15, 16, 18-21] It is now clearly established that about three-fourths of patients with metastatic disease can be cleared of disease, that several drugs are effective, and that once these patients remain free of disease for a year they are very unlikely to subsequently need further treatment. In fact, many of these women have had subsequent normal pregnancies. The price paid for this is slow, expensive, and potentially dangerous treatment, for each of the useful drugs is toxic. The most useful drugs are methotrexate, actinomycin D, 6-mercaptopurine, D.O.N.,* and combinations of drugs such as Li's triple therapy (methotrexate, actinomycin D, and chlorambucil).[16]

The largest series of trophoblastic disease patients treated with chemotherapy in the United States have been cared for at the National Institutes of Health in Bethesda. The findings of Dr. Hertz and his coworkers have been corroborated in smaller series by numerous workers using similar techniques. Several of the results of their experience will be described, for they represent the best results yet obtained with chemotherapy in this group of diseases.[20]

Most important is the fact that when both methotrexate and actinomycin D were available, the complete remission rate in 50 consecutive patients with metastatic gestational trophoblastic disease was 74 per cent. Although most of the metastases were pulmonary, there were others in the brain, liver, and other organs. The second observation is that though both methotrexate and actinomycin D can cause fatal toxic reactions, these can be avoided by selecting the correct drug and properly monitoring marrow, renal, and hepatic function during a course of therapy. Drug dosage can be decreased or the drug discontinued if there is evidence of early toxic reaction to a greater degree than expected. These drugs were given in intermittent 5-day courses of intensive therapy, with intervals allowed between courses for recovery from toxicity. Whether similar results could be obtained from chronic low-dose administration of these drugs is not known.

The two most important criteria for predicting response to chemotherapy were the level of HCG excretion at the time of admission and the duration of disease prior to the start of chemotherapy. In patients with a titer of less than 100,000 I.U. HCG per 24 hours, who were treated in less than 4 months from the apparent onset of disease, 94 per cent were cleared of their metastatic disease and are apparently cured. In the group with a titer of greater than 100,000 I.U. HCG per 24 hours, who were treated more than 4 months after the onset of disease, the comparable rate was 36 per cent. Chemotherapy is more effective the earlier that it is used.

These results of chemotherapy were clearly superior to any previous results with surgery alone in metastatic disease. Although there are isolated reports of regression of pulmonary metastases following hysterectomy, these were usually reported because of their rarity. Spontaneous regression of metastatic choriocarcinoma has been reported, but certainly does not occur often enough to keep this malignant disease from being regarded as one of the most rapidly growing and fatal of human neoplasms.

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*6-Diazo-5-oxo-L-norleucine.

Nonmetastatic Trophoblastic Disease

The proven effectiveness of chemotherapy in the treatment of metastatic disease raises the obvious question of its efficacy in nonmetastatic disease. The Bethesda series showed that it is effective in almost all patients with persistent molar disease, but cleared only 67 per cent of women with choriocarcinoma limited to the uterus.[10] A previous report by the author[15] further suggests that nonmetastatic choriocarcinoma may be less uniformly responsive to chemotherapy than persistent molar disease limited to the uterus. The great advantage of chemotherapy is that it allows the woman to retain her reproductive capacity. When a patient has been free of disease for a year, pregnancy is permitted. Successful pregnancy without recurrence of disease has been reported by several authors. Chemotherapy also is presumably effective in treating early metastases which may not be clinically evident.

The advantage in response rate of chemotherapy alone over surgery alone in patients with nonmetastatic disease is less marked than in metastatic disease. The cure of approximately 67 per cent of those with nonmetastatic choriocarcinoma is better than the 41 per cent cured by surgery alone, as reported in the Mathieu Chorionepithelioma Registry by Brewer.[1] The advantage to the chemotherapeutic treatment of nonmetastatic molar disease is primarily that it preserves reproductive function and also is more effective in the treatment of the 2 to 5 per cent of women with moles who subsequently develop choriocarcinoma.

RATIONALE FOR ADJUNCTIVE CHEMOTHERAPY

Efforts to combine the effectiveness of chemotherapy and surgery in the treatment of gestational trophoblastic disease have been proposed by several authors.[4, 5, 8, 15, 18, 21] Brewer[5] carried out hysterectomy in patients with metastatic disease after they had finished two or three courses of chemotherapy. This group had no better results than those treated with chemotherapy alone. The prophylactic administration of one or two courses of methotrexate to all women following surgical removal of a hydatidiform mole has been used in the Far East.[2, 18] This has resulted in a marked decrease in the subsequent development of malignant changes.

The temporal combination of chemotherapy and surgery was first reported by the author in 1965.[15] This program of surgery and adjunctive chemotherapy consists of the administration of a 5-day course of either methotrexate or actinomycin D. Surgery is carried out on the third day.

Several observations on the nature of trophoblastic diseases and the chemotherapeutic treatment form the rationale for this program. The first observation is that all trophoblastic tissue has the capability of invading blood vessels. Without this property, there could be no successful implantation. Both normal and abnormal trophoblastic cells tend to be deported in maternal vessels. The danger of deportation of tumor cells is increased by surgical manipulation. By carrying out surgery when there is an adequate blood level of drug, it is proposed that these cells will be more susceptible to its action than after they are enclosed in a fibrin

deposit. Another observation which makes this an ideal situation for combining surgery and chemotherapy is the previously described sensitivity of these tumors to both of these drugs. Careful control of drug toxicity is necessary. By the use of 80 per cent of full toxicity doses and careful monitoring of marrow, renal, and hepatic function before and during a course, this can be accomplished. The last justification comes from the observation that the earlier in the course of disease that chemotherapy is begun, the more effective it is. Using it at the first surgical procedure is employing it as early as possible.

Our first report of the results of this program showed the feasibility of the approach. No postoperative problems developed, nor was there spread of disease after 13 surgical procedures carried out on the third day of a 5-day course of methotrexate or actinomycin D. Goldstein[8] has recently reported the results of a similar approach in a series of 80 patients with molar pregnancy who were referred for treatment to the New England Trophoblast Center. Of the 39 women with molar pregnancy who underwent surgery during a course of chemotherapy, significantly fewer had a persistent titer than among 41 women with molar pregnancy who had surgery alone. Likewise, no metastases subsequently developed in the first group, but did occur in some of the patients undergoing surgery alone. Goldstein noticed no problems due to toxicity of the drug, even though he now employs a full dose of actinomycin D.

APPROACH TO VARIOUS CLINICAL PROBLEMS

Having said that it is our plan to carry out indicated surgery in patients with gestational trophoblastic disease during a course of chemotherapy, there is still the problem of defining the type of surgery to be carried out. It is not possible to list all of the possible clinical situations one encounters in these patients, but we will define the most common ones and outline our present approach to them.

Undelivered Hydatidiform Mole

This is the most common problem to be faced in women with gestational trophoblastic neoplasms. The diagnosis of this condition is not simple prior to the passage of tissue, but can be suggested both by history and laboratory tests.[13] However, the newly described technique of intra-amniotic dye injection[8] has greatly simplified this problem. The use of adjunctive chemotherapy at the time of removal of the mole is now limited to those patients who have passed recognizable molar tissue or have a characteristic appearance of a molar pregnancy by intra-amniotic dye injection. We have found this technique to be more useful than pelvic arteriography.

The method for removing the mole depends on the size of the uterus and the patient's age and desire for more children. In the past it has been advised that the uterus be emptied by dilatation and curettage if its size is less than that of a 12 weeks' gestation and by hysterotomy if larger. It has recently been reported that it is safer to treat all patients with intravenous pitocin until the mole is delivered vaginally and then follow this with curettage.[6]

There is still a place for hysterectomy in women who have completed their desired childbearing. This is particularly true in women 40 years old or more. These patients have been shown by Acosta-Sison to have a greater incidence of malignant sequelae to their molar pregnancy.[1]

The work-up of patients prior to starting chemotherapy is the same whether they are receiving it as adjunctive chemotherapy with surgery or as the only form of treatment. It includes the following blood studies: hemoglobin, hematocrit, white blood cell and differential count, absolute platelet count, serum glutamic oxaloacetic transaminase, bilirubin, and alkaline phosphatase. Routine urinalysis, chest x-ray, and a quantitative HCG assay on a 24-hour urine specimen are also carried out. If the patient is to receive methotrexate, the dose is 0.3 mg. per kg. body weight intramuscularly daily for 5 days. If actinomycin D is chosen, the dose is 10 micrograms per kg. body weight intravenously daily for 5 days. These represent approximately 80 per cent of the doses used when chemotherapy is given alone. It is not clear which drug is preferable except in patients with hepatic impairment, for whom actinomycin D is the drug of choice; impaired liver function markedly enhances methotrexate toxicity. Blood tests are repeated on the third day and the fifth day. The criteria for modifying the course are essentially those outlined by Ross.[20]

Surgery is carried out on the third day if clinically feasible. If a patient passes a small amount of molar tissue, it is possible to get these studies that day and start her chemotherapy the same day. She can then have a pitocin infusion and curettage after passage of the mole. If abdominal surgery is chosen, the ovarian enlargement due to hormonal stimulation should not be confused with tumor involvement. These theca-lutein cysts can reach enormous size, but they will regress when the HCG titer drops.

Follow-up on these patients consists of regular examinations plus quantitative HCG assays at intervals of 2 weeks. The time for determining when someone will be treated because of a persistent elevated titer will be discussed next.

Following Passage of a Hydatidiform Mole

The question is what to do to the patient who is referred for follow-up and treatment after her mole has been initially treated elsewhere. As mentioned earlier, some investigators are giving all of these women two courses of chemotherapy. Another approach has been to treat only those in whom the histology of the mole suggests aggressive behavior. Our policy has been to base treatment primarily on their HCG titers as well as clinical parameters such as uterine size and amount of bleeding. The importance of subsequent HCG titers in predicting the outcome of the disease in these women was first shown in a careful study by Delfs.[7] Approximately three-fourths of the women will have a normal level of gonadotropin 8 weeks after removal of the mole. Of the one-fourth still having an elevation at that time, half will clear spontaneously, but the others will go on to develop either invasive mole or choriocarcinoma. Thus, those with a titer elevation at 8 weeks have a 50 per cent chance of developing a clinically or histologically malignant condition. These pa-

tients and those whose titer rises before 8 weeks are treated as outlined in the next category.

Persistent Nonmetastatic Gestational Trophoblastic Disease

This category has several types of patients. It includes patients with molar disease who have a positive HCG titer 8 weeks after delivery of the mole or a rising titer before that. It also includes patients with the diagnosis of choriocarcinoma made by curettage following either a full-term normal delivery or a spontaneous abortion. The important criteria are that they have a histologic diagnosis of trophoblastic tissue, elevated HCG titer, and no evidence of metastases.

Treatment is again based not only on the histology but also age and desire for children. Women with a positive titer 8 weeks after passing a mole, who desire more children, should have curettage during a course of chemotherapy, with either methotrexate or actinomycin D. Surgery is not only therapeutic, but will be helpful in determining if the tissue now present is choriocarcinoma. The patient then receives subsequent courses of the drug until her titer is normal – that is, low enough to be consistent with pituitary origin. For older women whose family is complete, it is reasonable to carry out a hysterectomy during a course of chemotherapy. Any persistence of HCG titer more than 2 weeks after a hysterectomy is a strong indication of persistent metastatic disease.

The woman with choriocarcinoma limited to the uterus presents a somewhat more difficult problem. Although the results of treatment with chemotherapy alone (67 per cent cure) are better than those of surgery alone (41 per cent cure), the results are still not as good as when the tissue is still molar in character. Hertz's early series[10] showed that of six patients with nonmetastatic choriocarcinoma, four were cleared with chemotherapy alone, whereas the other two were cured by hysterectomy after several months of unsuccessful chemotherapy. The author's similar experience and observation of metastases occurring during chemotherapy of nonmetastatic choriocarcinoma have been reported.[15] It is reasonable to use chemotherapy alone in these women if they desire more children, but if they fail to respond to several courses of the first drug used, it is now advised that they have a hysterectomy during the first course of the second drug.

The administration of either actinomycin D or methotrexate to patients with nonmetastatic disease is essentially the same as in metastatic disease, except when the drug is used adjunctively with surgery. At that time only 80 per cent of full toxicity dosage is used.

Metastatic Gestational Trophoblastic Disease

Chemotherapy is the obvious treatment of choice for any patient with metastatic disease. The choice of drug, administration, criteria for changing drugs, and duration of treatment have been recently described[12, 20] and are based primarily on the experience of Hertz and his co-workers at Bethesda.

Proper treatment of these patients requires personnel experienced in chemotherapy and also laboratory facilities which can not only give ac-

curate reports on toxicity studies on the same day, but also carry out accurate and sensitive HCG assays. These needs are a strong argument for concentrating care of these patients in suitable facilities. The best results achieved in several large series of patients with metastatic disease have all been in centers with special interests and facilities to care for these women.[3, 5, 20]

Even though chemotherapy is the basic form of treatment for metastatic disease, these women will still require surgery. Approximately 20 per cent of the women undergoing chemotherapy for metastatic disease in Bethesda required some form of major surgery during their treatment.[14] The indications included control of hemorrhage, relief of urinary tract obstruction, and treatment of localized infection. Although surgery for these indications was not curative, it kept several patients alive long enough to be cleared of their disease by further chemotherapy.

UNUSUAL PRESENTING COMPLAINTS IN METASTATIC DISEASE

A discussion of adjunctive chemotherapy and surgery in this group of diseases would be incomplete without a brief mention of the many unusual ways in which metastatic trophoblastic disease can become manifest following any type of pregnancy. Although one is usually suspicious of continued tumor activity only after removal of a mole, one-half of the patients with choriocarcinoma develop it in a full-term pregnancy or early abortion. In these women the possibility of symptoms being due to choriocarcinoma is usually not considered.

To make the earliest possible diagnosis and thus to be able to start treatment as early as possible, one must consider the possibility of trophoblastic disease in any woman presenting with bleeding or metastatic tumor who has a history of recent pregnancy or menstrual irregularity consistent with an unrecognized abortion. If such a patient can be shown to have HCG titer by a sensitive method, it is possible to obtain appropriate treatment earlier.

Patients have been referred to me following the surprise diagnosis of choriocarcinoma at the following types of surgery: craniotomy for a brain tumor; small bowel resection because of gastrointestinal bleeding; exploratory thoracotomy to diagnose pulmonary metastases; and, finally exploration to determine operability of a "hepatoma" developing during pregnancy. In each patient the effective therapy was chemotherapy and it could have been started earlier if this rare but treatable condition had been considered and the gonadotropin assay ordered.

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REFERENCES

1. Acosta-Sison, H.: Indications for immediate hysterectomy without curettage in cases of hydatidiform mole. Amer. J. Obstet. Gynec., *81*:715-718, 1961.

2. Acosta-Sison, H.: Changing attitudes in the management of hydatidiform mole. Amer. J. Obstet. Gynec., *88*:634-636, 1964.
3. Bagshawe, K. D.: Trophoblastic tumors. Chemotherapy and developments. Brit. Med. J., 2:1303-1307, 1963.
4. Brewer, J. I., Smith, R. T., and Pratt, G. B.: Choriocarcinoma. Amer. J. Obstet. Gynec., *85*:841-843, 1963.
5. Brewer, J. I., Gerbie, A. B., Dolkart, R. E., Skom, J. H., Nagle, R. G., and Torok, E. E.: Chemotherapy in trophoblastic diseases. Amer. J. Obstet. Gynec., *90*:566-578, 1964.
6. Chan, D. P. C.: A plea against abdominal hysterectomy in the treatment of hydatidiform mole. Med. J. Malaya, *20*:36-38, 1965.
7. Delfs, E.: Quantitative chorionic gonadotropin. Prognostic value in hydatidiform mole and chorion epithelioma. Obstet. Gynec., *9*:1-24, 1957.
8. Goldstein, D. P., and Reid, D. E.: Recent developments in the management of molar pregnancy. Clin. Obstet. Gynec., *10*:313-322, 1967.
9. Hertig, A. T., and Mansell, H.: Tumors of the female sex organs. I. Hydatidiform mole and choriocarcinoma. *In* Atlas of Tumor Pathology. Washington, Armed Forces Institute of Pathology, 1956.
10. Hertz, R., Ross, G. T., and Lipsett, M. B.: Primary chemotherapy of nonmetastatic trophoblastic disease in women. Amer. J. Obstet. Gynec., *86*:808-814, 1963.
11. Holland, J. F., and Hreshchyshyn, M. M., eds.: Choriocarcinoma. U.I.C.C. Monograph Series, Vol. 3. Berlin and New York, Springer Verlag, 1967, Appendix 1.
12. Lewis, J., Jr.: Chemotherapy for metastatic gestational trophoblastic neoplasms. Clin. Obstet. Gynec., *10*:330-341, 1967.
13. Lewis, J. L., Jr.: Gestational trophoblastic neoplasms. Bulletin of the Sloane Hospital for Women, in press.
14. Lewis, J., Jr., Ketcham, A. S., and Hertz, R.: Surgical intervention during chemotherapy of gestational trophoblastic neoplasms. Cancer, *19*:1517-1522, 1966.
15. Lewis, J., Jr., Gore, H., Hertig, A. T., and Goss, D. A.: Treatment of trophoblastic disease. Amer. J. Obstet. Gynec., *96*:710-722, 1966.
16. Li, M. C.: Management of choriocarcinoma and related tumors of uterus and testis. Med. Clin. N. Amer., *45*:661-676, 1961.
17. Li, M. C., Hertz, R., and Spencer, D. B.: Effect of methotrexate therapy upon choriocarcinoma and chorioadenoma. Proc. Soc. Exper. Biol. Med., *93*:361-366, 1956.
18. Manahan, C. P., Manuel-Limson, G., and Abad, R.: Experience with choriocarcinoma in the Philippines. Ann. N.Y. Acad. Sci., *114*:875-880, 1964.
19. Ross, G. T., Goldstein, D. P., Hertz, R., Lipsett, M. B., and Odell, W. D.: Sequential use of methotrexate and actinomycin D in the treatment of metastatic choriocarcinoma and related trophoblastic diseases in women. Amer. J. Obstet. Gynec., *93*:223-229, 1965.
20. Ross, G. T., Hammond, C. B., Hertz, R., Lipsett, M. B., and Odell, W. D.: Chemotherapy of metastatic and non-metastatic gestational trophoblastic neoplasms. Tex. Rep. Biol. Med., 24(Suppl.):326-338, 1966.
21. Sung, H. C., Wu, P. C., and Ho, T. H.: Treatment of choriocarcinoma and chorioadenoma destruens with 6-mercaptopurine and surgery. Acta Un. Int. Cancr., 20:493-502, 1964.

Radiation Therapy in the Palliative Management of Patients with Recurrent Cancer of the Rectum and Colon

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Surgical resection of the primary lesion affords the optimum treatment for the patient with cancer of the colon and rectum. The results of surgical resection reveal a 50 to 60 per cent 5-year survival rate. In addition, there are a number of patients who have had palliative resections, plus an additional number who have nonresectable or inoperable cancer. All of these need care and relief of their pain and disability.

The most effective palliative tool in the management of the patient with recurrent cancer is surgery. Resection of localized disease in the liver, lung, abdominal wall, or anastomotic sites has proved to be an effective method of treating localized recurrence. In fact, pursuit of this method will yield an additional 10 per cent 5-year survival. The relief of pressure by excising gross metastases, relief of intestinal obstruction, and resection of metastases in the omentum and ovaries are additional methods of alleviating symptoms. However, the patient with disease amenable to local resection for cure or palliation is not among the majority. Most patients with recurrent cancer are in pain and have a definite disability due to nonresectable cancer.

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Radiation therapy has been used at Memorial Hospital in the treatment of cancer of the colon and rectum for 40 years. Preoperative radiation has been used in the treatment of adenocarcinoma of the distal colon and rectum. Radiation therapy directed to the involved area has been applied to patients with symptomatic recurrent disease and has been found to be an effective palliative agent.

MATERIAL

Four years ago a prospective study was started to evaluate the results of the use of radiation therapy for the palliative treatment of symptomatic nonresectable adenocarcinoma of the large bowel or rectum. Patients in this study group were Memorial Hospital clinic patients seen, evaluated, and assigned to treatment by an attending staff member on the Rectum and Colon Service. Patients were followed and examined at weekly intervals during the treatment period and at monthly intervals during the post-treatment evaluation. All patients were followed through January 1968, or until their death. The findings of these examinations and an evaluation of symptoms and patient response were recorded on work sheets. An objective evaluation of each patient's work quotient or performance status was also made in an attempt to evaluate the need for medication, the ability to perform normal activity, and the amount of necessary outside help or care. Ninety-four patients received radiation for palliation and were evaluated through the clinic.

A consecutive series of private patients from one office (H. W. W. and M. R. D.), who were seen, examined, followed, and assigned to treatment in this same period but within the private practice structure, were evaluated retrospectively by the use of the office charts. The same rules of evaluation were used and a retrospective indication of the performance status was made. There were 71 patients in this group. The total number of patients treated by radiation therapy for palliation in this study was 165 (Table 1).

Following a classification outlined by our chemotherapy service, we separated our patients into four groups depending on the extent of recurrence of their disease. These subdivisions were clinical patterns based on the major symptomatic area necessitating palliative treatment. Obviously, some crossover between groups existed, but the classification was determined by the major symptoms present. Thus, a patient with local symptomatic pelvic disease and with asymptomatic liver metastasis was classified as having local disease.

Local Disease Pattern. This group represents patients whose symptomatic recurrence could be readily encompassed by the usual ports

Table 1. *Palliative Radiation Therapy—Total Cases, 165*

Pattern of Disease	Private (71)		Ward (94)		Total (165)	
Local	41	58%	62	66%	103	62.5%
Hepatic	7	10%	15	16%	22	13.3%
Intra-abdominal	17	24%	10	11%	27	16.2%
Generalized	6	8%	7	7%	13	8%

available to the radiotherapist. It consisted almost entirely of patients with intra-pelvic disease causing pain due to pressure on the bladder, bowel, or sciatic nerve. Nonresectable perineal recurrences were included in this group, which comprised 41 private patients and 62 ward patients—a total of 103 patients or 62 per cent of the entire study group.

Hepatic Pattern. Those patients whose disease progression was characterized by massive liver enlargement are included in this group. Pain was a consistent factor; pressure on the stomach, diaphragm, and abdominal wall were major symptoms. Nausea and loss of appetite were common. The prime symptoms were due to the presence of metastatic liver disease, and asymptomatic liver metastases were not treated by radiation therapy. Jaundice was not a contraindication to treatment unless accompanied by hepatocellular damage advanced enough to indicate marked change in liver function and impending liver failure. Jaundice due to obstruction secondary to metastasis in the porta hepatis was found to be responsive to localized radiation therapy.

A total of 22 patients were included in this group, which represents only 13 per cent of the total. Patients with predominantly symptomatic liver metastasis and without other significant clinical manifestations of disease are less common.

Intra-abdominal Pattern. This group consists of those patients whose disease was characterized by diffuse peritoneal involvement. They had gross or miliary implants on the peritoneal surface, and usually extensive disease within the large or small bowel mesentery. Often there were bulky, palpable metastatic deposits. Abdominal wall or paracolostomy disease, if symptomatic, was treated locally, and such patients were included in this intra-abdominal group. Local pelvic disease or massive hepatic enlargement was not prominent. This group consisted of 27 patients (16 per cent). Radiation therapy was given to these patients in the area of predominant symptoms. Total abdominal radiation therapy for carcinomatosis was not performed. Ascites and the pressure symptoms secondary to the fluid accumulations were not felt to be amenable to external radiation therapy.

General Pattern. This last group includes the patients with generalized disease, with spread to lung, brain, and bone. Liver metastases were usually also present, although not a main cause of the symptoms. Bone metastases, when apparent, usually were evidence of widespread disease. Radiation therapy had a good local effect on the bone lesions, but patients with symptomatic brain metastasis did poorly with total brain irradiation. Diffuse pulmonary disease was felt to be untreatable by radiation therapy. Isolated symptomatic but nonresectable pulmonary lesions were treated. This group included the fewest patients, 13 in all or 8 per cent. Cancer of this pattern usually represents an advanced stage of a virulent process and is seldom amenable to local irradiation.

METHOD

All radiation therapy was administered by an experienced radiotherapist. Outline of treatment ports was done in consultation with the

referring surgeon, who in all cases was a member of the attending staff of the Rectum and Colon Service. Evaluation and recording of treatment results was based on weekly work sheets or on the records from the private office.

Telecobalt equipment was used most commonly. However, 250kV. radiotherapy equipment was used in a few of the reported cases. Areas were outlined depending upon the presence of disease and the presence of symptoms, and varied with the individual problem and the individual patient. In the case of localized pelvic disease a 20 × 20 cm. anterior and posterior port would be utilized. When indicated, a perineal port would be added. In patients with liver involvement, total hepatic irradiation was utilized, except that it was occasionally possible to protect a small portion of the unaffected liver by lead shielding.

The usual dose was a moderate one. No attempt was made in this palliative series to eradicate the disease by radiotherapy. For example, in the most commonly occurring instance of pelvic irradiation, a treatment course of 2000 to 2500 rads mid plane dose was delivered in 8 to 12 consecutive treatment days.

Almost all therapy was administered on an outpatient basis. Occasionally, patients for total liver irradiation were admitted for their treatment. Side effects were usually limited to malaise, anorexia, and nausea.

RESULTS

In the evaluation of treatment results, a graded format was used. Utilizing rather strict criteria, individual patients were placed into one of four categories based on their observed response to treatment.

Grade 1: Excellent response

1. Objective regression of palpable disease
2. Subjective improvement in complete pain relief, return to normal duties
3. Definite increase in performance status

Grade 2: Good response

1. Objective regression of palpable disease
2. Subjective improvement in pain relief, but on some medication, able to care for self
3. Increase in performance status

Grade 3: Fair response

1. No objective regression of disease
2. Some improvement in pain, remains on medication
3. No increase in performance status

Grade 4: No response

Each pattern of disease was then graded and the results tabulated.

In the local disease group, over one quarter of the patients had an excellent response, one half had a good response, and all but 5 per cent received some benefit from radiation therapy. As would be expected, these are the patients in whom cancer tends to remain localized and thus

Table 2. *Radiation Therapy in Patients with Local Disease*

RESPONSE	PRIVATE (41)		WARD (62)		TOTAL (103)	
1 Excellent	12	29%	15	25%	27	26%
2 Good	22	54%	32	52%	54	54%
3 Fair	6	14%	10	16%	16	15%
4 Poor	1	3%	4	7%	5	5%

lends itself to treatment directed at the area where the symptoms are arising. Although it was not the purpose of the study to report prolongation of life, the average life of a patient after treatment in this group was 18 months. The patients in the excellent response group had an average life of 30 months.

The hepatic group consisted of 22 patients, and 12 of them (slightly over half) received benefit from radiation therapy directed to the liver. Obviously, there are too few patients in any subgroup to make definite conclusions, but the fact that some people were helped with their massive painful hepatic metastasis is important. The average life span after treatment was about 1 year. Seven of these patients received more than one course of radiation to the liver.

As in the hepatic group, among patients in the intra-abdominal classification there are too few in any subgroup to draw any conclusions. However, over 50 per cent of the patients received some palliative effect as measured by an excellent or good response within our criteria. The average life expectancy was 11 months after treatment in this group.

There were only 13 patients with generalized spread. As would be expected, there were fewer able to be treated and the results were not as good—only a 46 per cent response. These patients usually have symptoms from their systemic disease, and only in a few is there some localization of the main symptom that can lend itself to local treatment by radiation. In this group of patients chemotherapy is probably the modality of choice, and radiation can only treat localized problems, such as bone pain. The average life following treatment in this group was 8 months.

DISCUSSION

Radiation therapy has not been widely accepted as an effective agent in the palliative treatment of adenocarcinoma of the large bowel. Many therapists carry their patients to the highest tolerated dose in order to achieve maximal antitumor effect. In theory, this may be desirable, but

Table 3. *Radiation Therapy in Patients with Hepatic Disease*

RESPONSE	PRIVATE (7)	WARD (15)	TOTAL (22)	
1 Excellent	0	2	2	9%
2 Good	2	8	10	45%
3 Fair	2	3	5	23%
4 Poor	3	2	5	23%

Table 4. *Radiation Therapy in Patients with Intra-abdominal Disease*

Response	Private (17)	Ward (10)	Total (27)	
1 Excellent	5	0	5	18%
2 Good	6	5	11	41%
3 Fair	3	4	7	26%
4 Poor	3	1	4	15%

treating to the tissue dose maximum (6000 rads) has in our opinion two definite drawbacks. First, such dosages preclude future radiation therapy to control symptoms. Sixty per cent of the patients with local disease, which in almost all instances means pelvic wall disease with pain and pressure symptoms, received more than one course of radiation therapy; many received three courses, and 10 per cent received more than three separately spaced courses of therapy with palliative effect. Second, the number and severity of complications increase many times when maximum doses (6000 rads) are reached. Except for a rare case, large bowel adenocarcinoma or its recurrence is not a radiocurable lesion, so that maximum dosage will rarely if ever effect a cure. However, when radiation is used in modest dosage (2000 rads) for the relief of symptoms, a significant palliative response can be obtained. In all types and in all cases treated, 50 per cent of patients with symptomatic recurrence received some benefit from suitably directed radiation therapy of modest dose.

The use of radiation therapy in this dose range (2000 to 2500 rads per treatment course) arouses considerable controversy among radiotherapists. However, we believe that this series represents a consecutive group of ward and private patients in whom radiation was effectively used as a palliative tool.

A word of caution is indicated. As in any modality, treatment failures increase when too much is expected of the method. We are quite careful about using too large a port. If there is metastasis to superficial node areas, such as the groin, the lymph nodes are better locally resected than treated with radiation therapy. The excessive use of perineal radiation is also to be avoided. Finally, any patient thought suitable for radiation therapy must first be thoroughly evaluated for the possibility of having surgically resectable recurrence. Many of our patients were explored in order to determine nonresectability. This is true for all areas, including

Table 5. *Radiation Therapy in Patients with Generalized Disease*

Response	Private (6)	Ward (7)	Total (13)	
1 Excellent	0	1	1	7%
2 Good	2	3	5	40%
3 Fair	3	1	4	30%
4 Poor	1	2	3	23%

perineum, pelvis, liver, and lung. In the past it has not been unusual for a patient referred to Memorial Center for radiation therapy for recurrent disease to be suitable for resection. In our present state of knowledge, extirpative surgery is the only known curative treatment. Surgery is also the best palliative tool for the suitable lesion, but we feel that radiation therapy should enjoy a greater role in palliative treatment. When used in the proper set of circumstances, it can be of substantial benefit to patients.

SUMMARY

Surgery is the treatment of choice for cure of adenocarcinoma of the colon and rectum. Surgery is the primary means of palliative treatment for large bowel cancer. Radiation therapy used judiciously and under very close follow-up and examination can play a major role in the palliative treatment of large bowel cancer. Of 165 patients undergoing palliative radiation therapy, more than 50 per cent had definite symptomatic and objective response. Localized disease, particularly intrapelvic cancer, lends itself to moderate dose radiation therapy, with 80 per cent of patients receiving definite symptomatic and objective response. The use of modest doses, well controlled and managed, is recommended for control of symptoms in patients with nonresectable cancer of the colon and rectum.

REFERENCES

1. Karnofsky, D. A., and Burchenal, J. H., *In* MacLeod, C. M., ed.: Evaluation of chemotherapeutic agents. New York, Columbia University Press, 1949, pp. 191-205.
2. Quan, S. H. Q., Deddish, M. R., and Stearns, M. W., Jr.: The effect of preoperative roentgen therapy in the ten and five year results of the surgical treatment of cancer of the rectum. Surg. Gynec. Obstet., *111*:507, 1960.
3. Stearns, M. W., Jr., Deddish, M. R., and Quan, S. H. Q.: Preoperative irradiation for cancer of the rectum and rectosigmoid. Preliminary review of recent experience (1957-1962). Dis. Colon Rectum, *11*:281, 1968.
4. Young, C., Ellison, R., Sullivan, R., Levick, S., Golby, R., Escher, G., Kaufman, R., Karnofsky, D. A., and Burchenal, J. H.: Evaluation of therapeutic response of large bowel cancer to the fluorinated pyrimidines in relation to clinical patterns. Proc. Amer. Assoc. Cancer Research, 3:164, 1960 (abstract).

Recognition and Treatment of Melanoma

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In a series of 267 patients with melanoma treated at Memorial Hospital prior to 1931, a 5-year survival rate of 12 per cent was reported in 1936 by Adair.[2] Later Pack, Gerber, and Scharnagle[52] reported a similar 10-year cure rate in patients treated before 1940, at which time a radical surgical approach became routine. In this 1952 report of 1190 patients, 40.5 per cent of patients who had no metastases to nodes remained free of tumor for more than 5 years, compared to only 14.1 per cent of those with lymph node metastases.

Eleven years later, McNeer and Das Gupta[43] reviewed a total of 804 patients with histologically verified melanoma of the trunk and extremities, observed between 1935 and 1955; of the total, 779 were determinate cases. At that time, primary melanoma was found to offer a 5-year survival rate of 71.5 per cent and a 10-year survival rate of 62 per cent, while stage II melanoma (tumors with regional node metastases) had a 12 per cent cure rate at 10 years. It is of course apparent that staging the tumors affects the cure rate remarkably, but the fact that 62 per cent of those patients whose melanoma was still localized to the primary site were cured in 10 years stands in opposition to the observation made 11 years earlier that although melanoma is the most accessible of all major forms of cancer, it has the unwelcome distinction of the lowest curability. Undoubtedly surgeons have contributed greatly to this remarkable improvement in the outlook for patients with melanoma, but of equal importance is the earlier detection of this tumor. Allen[3] observed that the histologic differentiation of pigmented lesions by biopsy occurs much earlier today than 30 years ago.

THE ROLE OF MOLES IN THE CONTROL OF MELANOMA

Melanoma is of special interest among neoplastic diseases because of the unusual nature of its precursor cell the melanoblast, or the

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*Attending Surgeon

melanogenocyte[5, 25] or melanocyte. Melanoma is preceded by a nevus in 24.8[10] to 71[36] per cent of cases. These figures indicate the importance of early differential diagnosis of the ubiquitous nevus. Allen[3] has stated that the junctional nevus is the most important key to the problem of melanoma and that it represents melanoma's precancerous phase.

Whether the melanoblast or melanogenocyte is of epidermal origin or of neuroectodermal origin is not within the scope of this paper. Allen has emphasized that the cutaneous melanoma should be regarded in any event as an epidermogenic lesion and as a carcinoma. Masson[11] and others acknowledge the epidermal location of these nevus and melanoma cells; the disparity lies simply in their regarding such epidermally located cells as nerve endings. Regardless of origin, Masson has emphasized that primary melanomatous tumors include those developing from freckles as well as from cellular nevi, and that all possess the same histologic characteristics and exhibit the same clinical evolution.

Concerning the specific origin of the melanocyte, the necessity to consider nevi is stressed by Masson.[11] He found the opinion of Becker and Allen regarding melanomas arising in cellular nevi to be fairly logical. They believed that the cellular nevus whose epidermis retains the characteristics of the junctional nevus, and especially those corresponding to the so-called "compound" nevus state, would be susceptible to neoplastic change. It is the early or small melanoma that affords the reward of clinical differentiation, and therefore the relationship of the active junctional nevus to the malignant melanoma is most important in the clinical control of melanoma.

Junctional nevi are relatively smooth, varying in color from tan to brownish black or slate-colored, and are almost always devoid of hair. They range in diameter from 2 or 3 mm. to several centimeters. Histologically, they show loss of cohesion in the basal layer of the epidermis, multiplication of clear cells of the basal layer (acanthosis), and nests or clusters of such cells. Stegmaier[60] estimates that 4 to 25 per cent of melanomas arise from nevi, usually at the junctional zone. This sign of activity appears in all nevi of childhood, in 60 per cent of nevi of the third decade, and in less than 10 per cent of nevi in persons over 50 years of age. A common and important feature of the junctional nevus is that toward the periphery of the lesion the changes are focal. As a result, there may be long skipped segments of normal epidermis between portions of the involved epidermis, as shown by Allen[3] in 1949. These segments may account for the local recurrence of melanoma.

Compound nevi show varying degrees of junctional change at the dermoepidermal junction, but also present the aging process of downward growth of melanoblasts with increasing degrees of stromal change in the dermis. This is a quantitative change in the life cycle, from the junctional nevus to the quiescent intradermal nevus. Kopf and Andrade[34] have stated that junctional proliferation can be found in 80 per cent of nevi if they are carefully scrutinized in serial sections. As long as the downward migration of melanoblasts occurs, the nevus will remain a compound nevus, but when it ceases, the nevus becomes an intradermal one. Allen holds that only 12 per cent of the intradermal nevi of adults are compounded with junctional change. Intradermal nevi are the

ubiquitous common moles. Their color varies from tan to brown, and they may produce a marked excrescence or an atrophic tag. They invade the dermis to varying degrees and contain not only melanoblasts but many similar cells no longer retaining dopa activity. These moles are resting nevi of only cosmetic interest.

A variant of the compound nevus is the juvenile melanoma, or epithelioid cell nevus.[33] While these nevi occur predominantly in prepubertal children, Allen[1] states that 15 per cent occur in adolescents or adults, and that these nevi show no greater vulnerability to cancerous change than any other compound nevus. Blue nevi are mentioned only to caution that their cellularity may vary greatly, and malignant transformation, although rare, may occur in them.[56]

THE INCIDENCE OF MELANOMA

One of the most trustworthy estimates of the incidence of melanoma was that of Macdonald,[38] who in 1948 gave the rate as 1.6 per 100,000 males and 2 per 100,000 females per year. Ekblad[23] has estimated that melanoma occurs in 1.8 persons in every 100,000, or, as extrapolated, that 1.8 melanomas are found among every 1.5 million nevi.

In a similar population, as reviewed by Macdonald in 1948, Clark and Macdonald[13] in 1953 reported that melanoma accounted for 1.5 per cent of the total cancer cases at the M. D. Anderson Hospital. More recently, the incidence was 3 per cent of that population.[40]

Basing their figures on hospital admissions, McSwain and associates[15] have indicated an increasing incidence of melanoma. They reported one patient with melanoma in every 2300 from 1925 through 1949, increasing thereafter (from 1950 to 1958) to one in every 1500.

More recently, in a comprehensive study of all patients with cutaneous malignant melanoma in Queensland, Australia, between 1963 and 1965, Davis, Harron, and McLeod[22] reported an incidence of 16.4 per 100,000 population, as compared to only 2.0 in England and 2.6 in the United States. They attributed part of this high incidence to increased public and professional awareness of the tumor, since 83.5 per cent of the lesions were smaller than 2.0 cm. In this Queensland analysis, the importance of suspicion, on the part of both physicians and laymen, as a factor in the increased reported incidence of the tumor is indicated by the fact that of 400 cutaneous lesions analyzed, 6.5 per cent were classified as in situ melanoma, 23.3 per cent were superficial, and 70.2 per cent were invasive. So important is this factor of awareness in the detection of early cancers that only 5 per cent of the patients had clinically involved lymph nodes when first seen. In prophylactic lymph node dissections conducted on 98 patients, only five positive instances of metastasis were found on routine sectioning, a figure considerably lower than is usually cited. The emphasis upon prevention will continue to increase reported incidence and at the same time improve survival rates. With the passing of a few more decades, it will prove to be one of the outstanding developments in the control of melanoma.

The Queensland report also emphasizes significant secondary factors in the occurrence of melanoma, such as the influence of race and com-

plexion on the incidence of moles and melanoma. This aspect has been studied by Pack, Davis, and Oppenheim,[51] who cited Lancaster's demonstration that the distribution of melanoma is consistent with the hypothesis that excess sunlight is an important predisposing cause. They reported that a majority of these tumors occur in patients who either are blond, or have blue or hazel eyes, or have fair skin with so few melanoblasts that they burn rather than tan on exposure to sunlight. They also stated that while the incidence of melanoma for Caucasians in the United States is somewhat under 1 per cent of all cancers, it is two to four times as great as the incidence in the Negro population. However, Macdonald[39] has noted an almost equal incidence in the two races in Texas.

While melanomas may occur at any age, Allen and Spitz[3] found that 62.7 per cent occurred in patients from 30 to 60 years of age, which are also the peak incidence ages for many other cancers. Location of these tumors was analyzed by Pack;[52] 27 per cent occurred on the lower extremities, 9.8 per cent on the upper, 2.9 per cent subungually, 24 per cent on the trunk, 22 per cent on the head and neck, and 10.9 per cent at a variety of less usual sites. In 2.4 per cent the primary site was unknown.

DIAGNOSIS

The diagnosis of melanoma utlimately depends upon the pathologist, but the selection of which nevi to remove and the index of suspicion depend upon the physician. The extent of the lack of clinical suspicion is reported by Becker,[7] who found that of 151 specimens on which the laboratory diagnosis of melanoma was made, a clinical diagnosis had been made by dermatologists or graduate students in this specialty in only 72 cases, or 48 per cent. Likewise, twice as many pigmented nevi were diagnosed clinically as microscopically, indicating that physicians make a benign diagnosis too readily and close their minds to the possibility of melanoma.

Surely any nevus which bleeds, expands, changes in color, or presents a variegation in color or outline should be removed. A 5 mm. margin of excision is adequate for these. However, if melanoma is suspected, it is my personal conviction that the lesion should be excised in the operating room, free of the trauma of local anesthesia. In the event of a positive frozen section biopsy, proper treatment can follow immediately upon closing the biopsy site. Local anesthesia and excision in the out-patient department is satisfactory in selected cases; 16 of 25 such operations at Memorial Hospital were successful, a definitive cure rate of 64 per cent.[12]

THE TREATMENT OF CUTANEOUS MELANOMA

At Memorial Hospital all patients are classified at the time of their original examination into three stages: the first group has localized tumors without metastases; the second group shows metastases confined to regional lymph nodes; and the third group includes all patients with disseminated melanoma.

The Treatment of Primary Melanoma

In the treatment of primary untreated melanoma, or melanoma removed by excisional biopsy within the previous month, the most important factor is wide surgical removal of the primary tumor. Even if an excisional biopsy has been done elsewhere, adequate exision must still be performed. Mundth, Guralnick, and Baker[46] have demonstrated the inadequacy of treatment "elsewhere;" in re-excision of the primary site of 78 patients out of 210 who had had previous excision, 43 patients or 55 per cent were found to have residual melanoma. Furthermore, of 55 patients who were reoperated upon but who were judged to have had an adequate prior excision, 20 patients or 36 per cent had residual tumor. Of 78 patients deemed to have had inadequate excisions, persisting tumor was found in 23. McNeer and Cantin[42] noted that previous inadequate treatment had been given to 60 per cent of the patients applying to Memorial Hospital for treatment of melanoma, and that recurrence had already developed in 27 per cent of the patients who had had inadequate local excision and in 58 per cent of those who had had electrodesiccation of their tumor.

The recommendation of Samson Handley[31] in 1907 for a minimal excision of 5 cm. around the melanoma is good advice. The International Group for the Clinical Study of Melanoma recommends a minimum of 3 cm. in all directions. We concur with the suggestion of Stehlin[61] that two thirds of the elliptical excision be in the direction of spread of the original lesion. A wide subcutaneous excision is done, which includes the fascia, as originally recommended by Handley. It is important that the initial excisional biopsy not be carried to the level of the fascia, so that in re-excision the fascia completely envelops the bed of the biopsy site.

In 1964, in a selected group of 112 patients whose melanomas were on the extremities (excluding the hands and feet) and on the lower abdominal wall, Olsen [48] noted that metastases to the regional lymph nodes developed in 14 of 31 patients – that is, 65 per cent – who had the fascia removed in excisional biopsy. But in 36 patients in whom the fascia was left intact, metastases were later observed in only 14 per cent. Daland,[17] Kragh and Erich,[35] and Mundth[46] have observed that omission of the underlying fascia from the biopsy specimen does not have the same effect on cure rates or recurrence rates as an adequately wide initial excision. A caution by a pathologist[1] is pertinent – although an adequate excision may be made around the tumor, frequently the depth of the tumor is underestimated. We have no evidence to show that a more comprehensive excision or re-excision has any deleterious influence.

Johnson's study,[32] showing that local occult metastases in the surrounding cutaneous lymphatics occur as frequently as metastases to regional nodes, indicates the necessity for as wide an excision of the lymphatic bed as possible. While at times it may seem unnecessary, considering that recurrences develop even after a peripheral excision of 5 cm. around a tumor, an excision of fascia is still in order so as to include a greater depth factor in a well-planned three-dimensional excision.

In some areas, such as the heel or the face, compromise in the extent of an excision is dictated by the area involved. As emphasized by Catlin,[12]

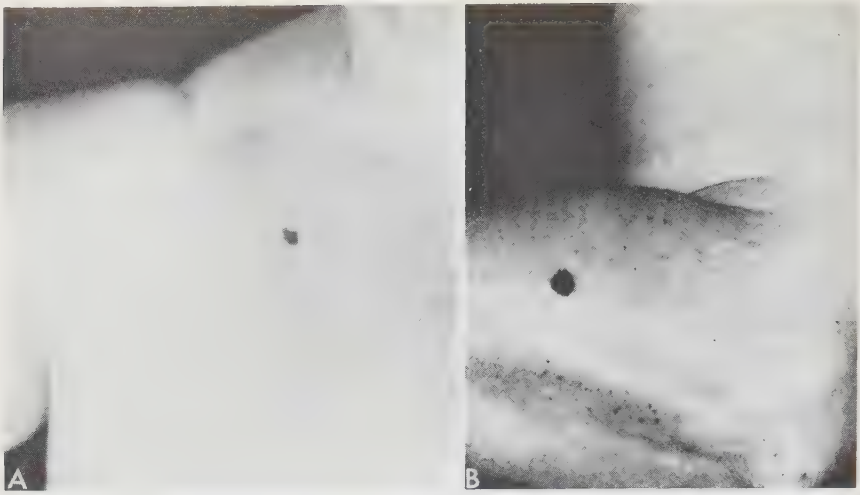

Figure 1. *A*, Early superficial melanoma over the clavicle. This 63-year-old woman noticed slow growth for a year. Her niece, a secretary in a pathology department, was aware of its possible diagnosis and referred her for treatment. It was less than 1 cm. in size, of variegated tannish-brown color, and on palpation was firmer than the surrounding skin. The diagnosis on excision was superficial melanoma, and a wide excision with closure by advancement of flap was done. Because it was less than 1 cm. in diameter and superficial in character, an elective node dissection was not done.

B, More advanced but still early melanoma of the forearm of a 55-year-old woman who noticed the expansion of this 1 cm. tumor over 6 months. It arose de novo. One physician had told her to "never to touch it or bother it." It "tingled" and was very sensitive. It was melanoma and not superficial.

the best policy is to do an adequate excision without any preconceived notions about closure. While the defect might be closed directly or with a rotated skin flap, a graft is used when neither of these two methods is feasible. The 5-year cure rate for patients treated by grafting in one study[12] was better than that for the control group.

For a superficial melanoma of 1 cm. of less, we feel that the usual local treatment accorded to melanoma is indicated to forestall the occasional unexpected aggressiveness of some of these tumors (Fig. 1). The closure of these wounds is usually made by a split thickness skin graft, whereas in some areas such as the back a transfer of flaps may be adequate for closure.

Because of the high incidence of the melanotic freckle of Hutchinson on the face, which of course is of a lower grade of malignancy, a lesser margin of resection may be sufficient here.[15, 21] However, in the study of McNeer and Cantin[12] on the failure of local treatment of melanoma, it is significant that in the region of the head and neck, where it is more difficult to do wide excisions of the primary lesion, there was a 15 per cent recurrence rate for primary melanomas and a rate of 45 per cent for those that presented regional node metastases. The over-all rate of recurrence was 21 per cent after so-called "wide" excision, with the restrictions implied in this region. On the scalp, extremely wide excisions are indicated; these must be replaced by grafts of split thickness.

For subungual melanoma, or melanoma on one of the digits, disarticulation at the metacarpophalangeal or metatarsophalangeal joint is usual, or amputation through the adjacent metacarpal or metatarsal bone.[18]

I do not employ regional perfusion techniques, and the experience of Stehlin and Clark[61] indicates no improvement in the treatment of primary malanoma with this method. They reported that the 5-year survival rate of 67 patients treated conventionally for stage I tumors was 70.5 per cent, as compared to 72.7 per cent of 107 patients who received perfusion with phenylalanine mustard. While Rochlin and Smart's[55] apparent cure rate with adjunctive or prophylactic chemotherapy was higher, theirs was not a definitive 5-year analysis.

Elective Node Dissections in Primary Melanoma

Since 1960, elective node dissections in stage I melanoma have been performed routinely on the Mixed Tumor Service at Memorial Hospital. In studying the incidence of metastases to accessible lymph nodes from melanoma of the trunk and extremities, progressive involvement of lymph nodes is revealed. Das Gupta and McNeer[19] observed that of all patients with primary melanoma of the trunk and extremities who ultimately succumb to the disease, 90 per cent have metastatic melanoma in the ipsilateral regional lymph nodes at autopsy, as compared with an incidence of 40 per cent in those studied during life. Stehlin, Hills, and Rufino[62] reported that in 67 per cent of patients with disseminated tumors, the advancing disease involved the regional lymph nodes. This suggests the need for early examination of regional lymph nodes for "probable small metastases."[11] McNeer and Das Gupta[43] found that in 23 per cent of 335 patients who underwent node dissections before the nodes were considered suspicious, but in whom the pathologist verified metastasis, there was a 52.6 per cent 5-year survival rate, as opposed to a 19 per cent rate for those with dissections done for obviously involved nodes. Lane, Lattes, and Malm[36] reported similarly that 41 per cent of patients who underwent elective dissection proved to have clinically undetected metastases; they gave a 71 per cent cure rate.

Mundth et al.[46] report a 59 per cent cure rate in 18 patients whose nodes were clinically negative but histologically positive, as compared to 22 per cent when dissection was done for therapeutic reasons, figures similar to our experience. The survival rate with elective node dissection was 76 per cent in stage I disease, with a 10-year cure rate of 62 per cent. The 10-year survival rate of patients with clinically negative but pathologically verified nodes having dissections was 38 per cent, as opposed to 64 per cent if the nodes were histologically negative.

A regional basis for elective node dissections is supplied in the data from our hospital by Fortner, McNeer, and Das Gupta.[27] Their study of melanoma on the trunk showed that 21.9 per cent of 82 patients with clinically negative nodes harbored metastases found by elective dissection. However, in a series of 47 patients with clinically negative nodes subjected to groin dissection for melanoma of the lower extremity,

38 per cent had positive nodes.[26] Also, in a group of 228 patients with melanoma of the feet, where regional factors make for a poor prognosis, 69 had a primary tumor intact with simultaneous node metastases. In seven patients, or 10 per cent, this was not clinically apparent, and their dissection was presumed to be "prophylactic." Their survival rate was 28.8 per cent, as opposed to a rate of 15 per cent in those with clinically obvious metastases.

Of significance in the study of node dissection in the groin is the fact that among 167 patients who had positive nodes, the over-all 5-year survival rate was 78.7 per cent in 39 patients who had elective dissections, but whose nodes were found to show no metastases. In all subgroups of this latter study, a higher survival rate for those patients with node-negative disease was sustained than obtains for stage I melanoma treated at the primary site only. This would suggest that there must be a few patients in whom node metastases are present but cannot be verified by the pathologist. The early removal of such nodes has contributed to cures. These findings support the observation of Southwick[59] that for us to be justified in deferring regional node dissection until there is evidence of metastasis, the survival rate for such patients would have to be good as it is for those with clinically negative but pathologically detected metastases. The indeterminate extent of early metastases of melanoma makes it mandatory to operate on the principle of removing all of the probable sites of involvement. In planning an operation for melanoma, recourse to the study of Das Gupta and McNeer[19] on the incidence of metastases to accessible lymph nodes has real therapeutic significance.

An important consideration in the role of elective regional lymphadenectomy is the principle of in continuity vs. disparate dissection. This was discussed by Pack, Scharnagle, and Morfit[54] in 1945 and was recently reviewed by Conway, Hugo, and McKinney.[14] Even those who oppose elective adenectomy practice the procedure if the primary lesion is near the lymph nodes and thus can be excised in continuity. The principle is a valid one, and yet our evaluation in the groin indicated that when nodes were positive, 28 per cent of such patients survived 5 years, as opposed to 22 per cent of those who had discontinuity procedures.[26]

Multiple Primary Melanoma

Allen[3] defined primary melanoma as one still showing junctional change in it or in the adjacent skin, in contrast to the metastatic lesion, in which the melanoma is entirely beneath the skin with no evidence of junctional change over it. By this definition, 16 of 1250 patients at Memorial Hospital were found to have multiple primary melanoma.[53] This is a little more than 1 per cent, an incidence similar to that recently reported at the M. D. Anderson Hospital.[65] These findings corroborate Allen and Spitz's observation[5] that a patient with a cutaneous melanocarcinoma is likely to show evidence of activation of junctional nevi in the skin of other parts of the body, as though some circulating hormonal influence is exerted on moles elsewhere, occasionally with the production of multiple primary tumors.

Figure 2. *A*, The foot of a 72-year-old woman with the history of a blister of 3 weeks' duration. She had opened the blister and stated that it discharged bloody fluid. The ulcer measures 8 mm. The area of suture on the lateral aspect of the heel, thought to be a nevus, also revealed melanoma. Two other cornified discolored areas were thought to be melanoma but were not. No residual tumor was found after a wide excision and split thickness skin graft. A superficial groin dissection showed no metastases in nodes or frozen section, and no metastases were discovered after a radical groin dissection.

B. Second primary melanoma on the lower thigh which had been overlooked by both the patient and previous examiners. It was 1 cm. in diameter, brown and variegated in color, and slightly elevated. After local excision, the diagnosis was malignant melanoma with focal ulceration and residual benign nevus, considered primary at this site. The patient refused further treatment.

It is therefore important to follow the patient with a melanoma and to regard him as likely to need care for a second one, besides anticipating his developing a second unrelated primary cancer. The treatment of the second primary melanoma is governed by the principles ordinarily obtaining (Fig. 2).

MELANOMA WITH METASTASES CONFINED TO THE REGIONAL LYMPH NODES

If the regional lymph nodes are palpably enlarged and clinically suspicious, the chances are that the nodes will be involved with metastases. Gumport and Meyer[30] noted a false positive error in diagnosis in the evaluation of 29 per cent of their patients, whereas 9 of 40 patients with microscopically negative nodes were erroneously considered positive, an error of 23 per cent. At Memorial Hospital the degree of clinical error is similar. Of 220 patients with clinically suspicious nodes, 77 per cent were proved to have metastases on pathologic examination.[26]

If the regional nodes are suspicious, we perform a dissection without prior biopsy. There is little question about its necessity at this stage of the tumor's spread, though many surgeons perform their duty with little hope of success. At Memorial Hospital, in the 20-year period from 1935 to 1955, 295 of 779 determinate melanomas were in stage II. Nineteen per cent of the patients in this group were 5-year survivors; the figure dropped to 17 per cent at 7 years and to 12 per cent at 10 years.[43]

There is a relationship between the number of nodes involved and the prognosis. Guiss and Macdonald[29] noted that 87 per cent of patients with microscopically negative nodes who had regional node dissection survived tumor-free at 5 years; when a single nodes was positive, 53 per cent survived 5 years. However, when multiple nodes were positive, only 21 per cent survived 5 years. Further evidence is in a previous report of groin dissections at Memorial,[26] in which 39 of 167 patients with histologically positive nodes, or 23.3 per cent, survived 5 years. In 132 of these patients only the nodes in the superficial compartment were involved; their 5-year survival rate was 41.6 per cent. Of 46 patients, however, with both superficial and deep node metastases, only four, or 8.7 per cent, survived 5 years. This latter figure is of importance in analyzing reports of adjuvant perfusion treatment, in which those patients with extension of metastases above the inguinal ligament are excluded from the assessment of end results. It is not entirely true that patients with clinically positive iliac node metastases present a situation in which cure is improbable under any circumstances.[55]

Inadequate treatment of unrecognized tumor cells in the primary site, with subsequent spread by tumor embolization[1, 67] or by centripetal permeation, may be responsible for metastasis, or possibly the cause is a reversal of this phenomenon—the retrograde dissemination from blocked lymph nodes. That the latter may be the predominant cause is supported by the finding of Stehlin and Clark[61] that 9 out of 10 patients who have recurrences after perfusion have proven metastases to the regional lymph nodes. This experience is similar to ours in reviewing the metastases from a single distant site on an extremity (the foot), in which

14 of 56 patients (25 per cent) who underwent groin dissection had diffuse recurrences in the extremity, and all except one had proven metastases.[10]

The role of regional perfusion with chemotherapeutic agents in treating regional node metastases of melanoma is difficult to assess. It is generally agreed that lymphedema in the lower extremity is a postoperative complication of practically every groin dissection, although lymphedema is of little consequence after axillary dissection. Stehlin and Clark[61] have reported a recurrence rate of 23 per cent after axillary dissection with conventional treatment, as compared to 10 per cent after axillary dissection with perfusion. The corresponding rates in the lower extremity after groin dissection were 39 and 20 per cent. It is postulated that the occurrence of a greater proportion of metastatic nodules on the trunk and lower extremities can be explained by the fact that the intervening lymphatic plexus is longer and there is greater opportunity for entrapment of tumor emboli. Johnson[32] has observed that if propylactic removal of lymph nodes, by creating lymphedema, facilitates entrapment of metastases, the head and neck and the trunk, where the long path is unpredictable and prophylactic resection is often not done, are areas where this hypothesis may be tested. In his series the reverse was true. In combining groups, there was one satellite case in which 15 prophylactic resections were done as compared to four of 30 in which there were no dissections. In the M. D. Anderson Hospital, it is reported that 8 of 10 patients who have recurrence after perfusion have concomitant distant metastases. The ratio is lower among those treated conventionally, which leads to the observation that perfusion delays the appearance of recurrences until the distant metastases become overwhelming, and that the 5-year survival rate after perfusion is at least equal to that after conventional treatment and, perhaps, will prove to be 10 per cent higher. It is of special importance in this experience that perfusion has materially reduced the incidence of recurrence within the lower extremities.

As stated by Lawrence,[37] until the experimental series initiated by Creech and Stehlin has been expanded and followed for a number of years, regional chemotherapy in the primary treatment of curable melanoma cannot be evaluated realistically, and it would seem wise to adhere to established surgical principles. Beyond the use of chemotherapy, the intralymphatic administration of radioactive isotopes for treating malignant melanoma is an ingenious approach, although still clinically unproved. In general, the disadvantage of irradiation as a curative procedure for melanoma contraindicates this sort of treatment. Ariel[6] concluded that the disadvantage of this treatment is that a malignant melanoma does not concentrate the radioactive nuclide. This ingenious mode of therapy would provide effective irradiation only to small deposits of melanoma, but its value remains to be determined.

THE ROLE OF AMPUTATION IN MELANOMA

When melanoma is recurrent and also presents regional node metastases, an ominous situation exists: only 12 per cent of such patients

are free of tumor at the 5-year mark with conventional means of treatment.[10] In this situation, early major amputation is indicated to avoid disseminated recurrences in the extremity after regional node dissection. Wide excision of the primary melanoma and dissection of the regional lymph nodes in continuity is practically sound and widely accepted. We concur with the view that if in continuity dissection is not feasible, the only method of treatment whereby one can be assured that recurrences within the extremity will not subsequently appear is amputation of the entire extremity.[61] We cannot understand why this policy is not recommended when there is an intact primary lesion or a recurrent one with positive regional lymph node metastases. Surgeons who do not hesitate to recommend amputation for bone or soft tissue sarcoma will not apply the same treatment for melanoma, which has such an ominous prognosis at this stage.

McPeak and his associates [11] at Memorial Hospital have reviewed the course of 46 patients treated by major amputation for primary melanoma on the lower extremity and have found that 16 (34.8 per cent) survived 5 years or more; only 25 per cent of a small series with melanoma of the upper extremity treated in such fashion were 5-year survivors. All patients in the first group who survived had no metastases above the inguinal ligament, but all patients, whether they had positive iliac nodes or not, were included for analysis. A separate analysis of the results of perfusion in this situation excludes those patients with metastases above the inguinal ligament as patients for whom cure was improbable under any circumstances. Eleven of 30 patients with secondary melanoma had no sign of the disease 4 or more years after treatment.[16]

Our general practice on the Mixed Tumor Service, in the face of recurrence or metastasis which is multiple and distal to a major joint separating the primary site from the regional lymphatic drainage area (that is, the elbow or knee), is to amputate at the highest proximal joint. A regional node dissection is done at the same time. Primary melanoma below the elbow or knee cannot be treated in continuity except by amputation. In these instances, amputation is considered only after a painstaking clinical examination for skin or soft tissue metastases or distant nodes. Also, stereoscopic frontal and lateral roentgen study of the chest must give negative findings, as must bone marrow studies, and preliminary exploratory laparotomy must reveal no metastases which would deny an amputation the hope of cure.

MELANOMA OF UNKNOWN PRIMARY ORIGIN

In 1933, Ewing[10] discussed the finding of groups of nevus cells in the septa of an axillary lymph node and suggested that melanoma might originate there. Another explanation for their presence might have been the spontaneous regression of a small primary melanoma. Stout[66] warned that metastases can be found in lymph nodes when no primary melanoma can be discovered. Pack and Miller[50] found this to occur in 2.4 per cent of patients (29 of 1190), and later, Das Gupta, Bowden, and Berg[20] reported it in 37 of 992 patients, or 3.7 per cent, in a 23-year survey.

In 13 of these patients, the disease was incurable. In 461 patients at the M. D. Anderson Hospital, metastasis with no detectable primary occurred in 40 (8.7 per cent).[62]

The significant consideration is that when the melanoma was confined to one regional node basin in these reports, node dissection gave a cure rate as high as in other obvious nodal metastases for melanoma —29.7 per cent. When the metastases were further restricted to a single lymph node depot, 10 of 24 patients were definitive 5-year cures.

DISSEMINATED MELANOMA

McNeer and Das Gupta,[43] analyzing the behavior of primary melanoma, found that 19 per cent of these tumors disseminated by the bloodstream without evidence in regional lymph nodes. This figure is similar to the 25 per cent noted in the M. D. Anderson series,[62] in which one of every four patients came to a major surgical procedure because of such dissemination and for palliative purposes (Fig. 3). In general, systemic therapy has not been rewarding; as noted by Creech and Krementz,[16] it does not affect the natural course of the disease, even though improvement may occur. Ninety-nine per cent of these patients will have died within 2 years after reaching this stage.[43]

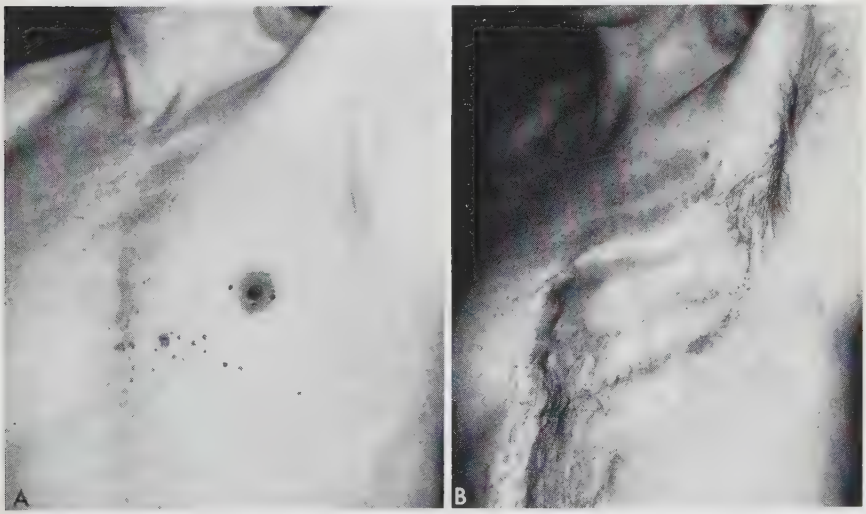

Figure 3. *A*, The chest wall of a 40-year-old man with in-transit metastases on the chest wall. Three years earlier, excision of a melanoma over the costal margin had been done, and axillary dissection showed metastases in three lymph nodes. A biopsy of one of these lesions was reported variously as "activated junctional nevus," benign nevus, and melanoma. Wide exision with skin graft replacement was performed and an axillary dissection completed in continuity. There were numerous skin nodules of melanoma and negative nodes. A recurrence on the lower chest was excised and replaced with a skin graft after 2 years.

B, Three and one half years later, at which time the patient was subjected to a right axillary dissection for a solitary metastases. This is considered a palliative procedure.

FACTORS OF AGE AND SEX IN MELANOMA

The influence of age on the diagnosis of pigmented tumors in children with juvenile melanoma has been noted. True malignant melanoma may also appear in children, however. Allen[1] has said that while such tumors may not be differentiable from those in adults, they can be distinguished histologically from juvenile melanoma. He reported that of 29 melanomas in children, 15 were fatal and eight others metastasized. At present, 15 cases occurring at Memorial Hospital from 1928 to 1968 are being analyzed. Skov-Jensen, Hastrup, and Lambrethsen[57] reviewed 43 similar cases in the literature and added two of their own. They found that the 3-year survival rate in children was similar to the 5-year cure rate in adults. (Children with melanoma are given the same treatment as adults.) These authors call attention to the high likelihood of melanomas arising in nevus pigmentosus giganticus and to the poor prognosis in these instances because of late diagnosis. Pack and Davis,[49] in a review of recent literature, noted this occurrence in 10 of 57 giant nevi (17.5 per cent).

Another factor in the management of melanoma is pregnancy. At Memorial Hospital, George, Fortner, and Pack[28] have not been able to sustain a previous impression of the deleterious effect of pregnancy. While 115 pregnant women had a higher incidence of node metastasis than 330 nonpregnant women who were of similar ages, their survival rate was 47 per cent, comparable to that of other patients at the time of the survey. However, there is probably some hormonal influence in the growth of melanoma, as has been shown by Nathanson, Hall, and Farber,[47] who noted a better prognosis for females – 38 per cent 5-year survival as compared to 22 per cent for males. They also reported that in the premenopausal fourth decade in women, survival was twice that for men, an advantage that was lost in the fifth and sixth decades. They felt that "femaleness" improved prognosis, especially in the hormonally active premenopausal period, while "maleness" tended to promote initiation of melanoma and to lead to a lower survival rate once the tumor became established.

This matter is not clear, however. Black and Hartwell's[9] statistical analysis of a similar number of patients, while confirming an increased incidence in males and the effect of age on survival rate, failed to show better survival in either sex. These authors, however, concluded that adequate treatment does influence the course of melanoma and results in increased survival rates, so that one must reject a philosophy of therapeutic nihilism in favor of therapeutic orthodoxy.

CONCLUSION

Reappraisal of the results of treatment of melanoma has been a prime consideration of the Gastric and Mixed Tumor Service at the Memorial Cancer Center. Each decade has shown the advantage of more radical and adequate surgery in the constantly increasing salvage of patients.

Early recognition of the tumor is made possible by awareness and suspicion of pigmented nevi and the excision of any suspicious nevi. Suspicion on the part of the patient with a nevus, or of his physician, should be converted to the exactitude of an excisional biopsy.

The indeterminate extent of early metastases, either local or regional, makes it mandatory to operate on the principle of removing all probable sites of involvement early in the course of melanoma. Early dissemination is apparent only to the discerning and careful pathologist.

REFERENCES

1. Ackerman, L. V., and del Regato, J. A.: Malignant melanomas of the skin. *In* Cancer: Diagnosis, Treatment and Prognosis. St. Louis, C. V. Mosby Co., 1947, Chapter VI.
2. Adair, F. E.: Treatment of melanoma. Report of four hundred cases. Surg. Gynec. Obstet., 62:406-409, 1936.
3. Allen, A. C.: A reorientation on the histogenesis and clinical significance of cutaneous nevi and melanomas. Current status. Cancer, 2:28-56, 1946.
4. Allen, A. C.: Juvenile melanomas. *In* Riley, V., and Fortner, J. G., eds.: The Pigment Cell—Molecular, Biological and Clinical Aspects. Ann. N.Y. Acad. Sci., *100*:29-48, 1963.
5. Allen, A. C., and Spitz, S.: Malignant melanoma. A clinicopathological analysis of the criteria for diagnosis and prognosis. Cancer, 6:1-45. 1953.
6. Ariel, I. M.: Progress in cancer: Lymphography and endolymphatic administration of radioactive isotopes for treating cancer. N.Y. State J. Med., *68*:1247-1269, 1968.
7. Becker, S. W., Jr.: Pitfalls in the diagnosis and treatment of melanoma. Arch. Dermat. Syph., *69*:11-30, 1954.
8. Becker, S. W., Jr., Fitzpatrick, T. B., and Montgomery, H.: Human melanogenesis: Cytology and histology of pigment cells (melanodendrocytes). A.M.A. Arch. Dermat. Syph., 65:511-523, 1952.
9. Black, G. E., and Hartwell, S. W., Jr.: Malignant melanoma: A study of 217 cases. I. Epidemiology. Ann. Surg., *154*:74-87, 1961.
10. Booher, R. J., and Pack, G. T.: Malignant melanoma of the feet and hands. Surgery, *42*:1084-1121, 1957.
11. Brown, J. B., and McDowell, F.: General considerations. *In* Neck Dissection. Springfield, Ill., Charles C Thomas, 1954, pp. 3-20.
12. Catlin, D.: Cutaneous melanoma of the head and neck. Amer. J. Surg., *112*:512-521, 1966.
13. Clark, R. L., Jr., and Macdonald, E. J.: The natural history of melanoma in man. *In* Gordon, M., ed.: Pigment Cell Growth. New York, Academic Press, 1953, pp. 139-148.
14. Conway, H., Hugo, N. E., and McKinney, P.: Excisions of glands in continuity for malignant melanoma. Arch. Surg., *94*:129-133, 1967.
15. Costello, M. J., Fisher, S. B., and DeFeo, C. P.: Melanotic freckle—lentigo maligna. A.M.A. Arch. Surg., *80*:753-771, 1959.
16. Creech, O., and Krementz, E. T.: Regional perfusion in melanoma of the limbs. J.A.M.A., *188*:855-858, 1964.
17. Daland, E. M.: Malignant melanoma—personal experience with 170 cases. New Eng. J. Med., *260*:453-460, 1959.
18. Das Gupta, T., and Brasfield, R.: Subungual melanoma. 25-Year review of cases. Ann. Surg., *161*:545-552, 1965.
19. Das Gupta, T., and McNeer, G. P.: The incidence of metastasis to accessible lymph nodes from melanoma of the trunk and extremities. Its therapeutic significance. Cancer, *17*:897-911, 1964.
20. Das Gupta, T., Bowden, L., and Berg, J.: Malignant melanoma of unknown primary origin. Surg. Gynec. Obstet., *117*:341-345, 1963.
21. Davis, J., Pack, G. T., and Higgins, G. K.: Melanotic freckle of Hutchinson. Amer. J. Surg., *113*:457-463, 1967.
22. Davis, N. C., Herron, J. J., and McLeod, G. R.: Malignant melanomas in Queensland; analysis of 400 skin lesions. Lancet, 2:407-412, 1966.
23. Ekblad, G. H.: Treatment of pigmented moles. A.M.A. Arch. Dermat. Syph., *70*:399-410, 1957.
24. Ewing, J.: Lecture XIX. *In* Lectures on Tumor Pathology. New York, Barnes Press, 1933, p. 108.
25. Fitzpatrick, T. B.: Human melanogenesis: The tyrosinase reaction in pigment cell neoplasms, with particular reference to the malignant melanoma. Preliminary report. A.M.A. Arch. Dermat. Syph., 65:379-391, 1952.

26. Fortner, J. G., Booher, R. J., and Pack, G. T.: Results of groin dissection for malignant melanoma in 220 patients. Surgery, *55*:485-494, 1964.
27. Fortner, J. G., McNeer, G. P., and Das Gupta, T.: Primary malignant melanoma of the trunk. An analysis of 194 cases. Ann. Surg., *161*:161-169, 1965.
28. George, P. A., Fortner, J. G., and Pack, G. T.: Melanoma with pregnancy; report of 115 cases. Cancer, *13*:854-859, 1960.
29. Guiss, L. W., and Macdonald, I.: The role of regional lymphàdenectomy in treatment of melanoma. Amer. J. Surg., *104*:135-142, 1962.
30. Gumport, S. L., and Meyer, H. W.: Treatment of 126 cases of malignant melanoma. Ann. Surg., *150*:989-992, 1959.
31. Handley, W. S.: The pathology of melanotic growths in relation to their operative treatment. The Hunterian Lecture, II. Lancet, *1*:996-1003, 1907.
32. Johnson, R. E.: Occult lymphatic metastases in malignant melanoma of the skin. Ann. Surg., *146*:931-956, 1957.
33. Kernen, J. A., and Ackerman, L. V.: Spindle cell nevi and epithelioid nevi (so-called juvenile melanomas) in children and adults. A clinicopathologic study of 27 cases. Cancer, *13*:612-624, 1960.
34. Kopf, A. W., and Andrade, R.: Histologic study of the dermoepidermal junction nevi, employing serial sections. *In* Riley, V., and Fortner, J. G., eds.: The Pigment Cell—Molecular, Biological and Clinical Aspects. Ann. N.Y. Acad. Sci., *100*:200-222, 1963.
35. Kragh, L. V., and Erich, J. B.: Malignant melanomas of the head and neck. Ann. Surg., *151*:91-96, 1960.
36. Lane, N., Lattes, R., and Malm, J.: Clinicopathological correlations in a series of 117 malignant melanomas of the skin of adults. Cancer, *11*:1025-1043, 1958.
37. Lawrence, W.: Current status of regional chemotherapy, II. Results. N.Y. State J. Med., *63*:2518-2534, 1963.
38. Macdonald, E. J.: Malignant melanomas in Connecticut. *In* Miner, R. W., and Gordon, M., eds.: The Biology of Melanomas. Ann. N.Y. Acad. Sci., *4*:71-81, 1948.
39. Macdonald, E. J.: Malignant melanoma among Negroes. *In* Gordon, M., ed.: Pigment Cell Biology. New York, Academic Press, 1959, pp. 171-181.
40. Macdonald, E. J.: The epidemiology of melanoma. *In* Riley, V., and Fortner, J. G., eds.: The Pigment Cell—Molecular, Biological and Clinical Aspects. Ann. N.Y. Acad. Sci., *100*:4-17, 1963.
41. Masson, P.: My conception of cellular nevi. Cancer, *4*:9-38, 1951.
42. McNeer, G. P., and Cantin, J.: Local failure in the treatment of melanoma. The Janeway Lecture, 1966. Amer. J. Roentgenol., *99*:791-808, 1967.
43. McNeer, G. P., and Das Gupta, T.: Prognosis in malignant melanoma. Surgery, *56*:512-518, 1964.
44. McPeak, C. J., McNeer, G. P., Whiteley, H. W., and Booher, R. J.: Amputation for melanoma of the extremity. Surgery, *54*:426-431, 1963.
45. McSwain, B., Riddel, D. H., Richie, R. E., and Crocker, E. F.: Malignant melanoma. Ann. Surg., *159*:967-975, 1964.
46. Mundth, E. D., Guralnick, E. A., and Baker, J. W.: Malignant melanoma—a clinical study of 427 patients. Ann. Surg., *162*:15-28, 1965.
47. Nathanson, L., Hall, T. C., and Farber, S.: Biological aspects of human malignant melanoma. Cancer, *20*:650-655, 1967.
48. Olson, G.: Removal of fascia—cause of more frequent metastasis of malignant melanoma of the skin in regional lymph nodes. Cancer, *17*:1159-1164, 1964.
49. Pack, G. T., and Davis, J.: Nevus giganticus pigmentosus with malignant transformation. Surgery, *49*:347-354, 1964.
50. Pack, G. T., and Miller, T. R.: Metastatic melanoma with indeterminate primary site—report of two instances of long-term survival J.A.M.A., *176*:55-56, 1961.
51. Pack, G. T., Davis, J., and Oppenheim, A.: The relation of race and complexion to the incidence of moles and melanoma. *In* Riley, V., and Fortner, J. G., eds.: The Pigment Cell—Molecular, Biological and Clinical Aspects. Ann. N.Y. Acad. Sci., *100*:719-742, 1963.
52. Pack, G. T., Gerber, D. M., and Scharnagle, I. M.: End results in the treatment of malignant melanoma. A report of 1190 cases. Ann. Surg., *136*:905-911, 1952.
53. Pack, G. T., Scharnagle, I. M., and Hillyer, R. A.: Multiple primary melanoma. A report of sixteen cases. Cancer, *5*:1110-1115, 1952.
54. Pack, G. T., Scharnagle, I. M., and Morfit, M.: The principle of excision and dissection in continuity for primary and metastàtic melanoma of the skin. Surgery, *17*:849-866, 1945.
55. Rochlin, D. B., and Smart, C. C.: Treatment of malignant melanoma by regional perfusion. Cancer, *18*:1544-1550, 1965.
56. Rodriguez, H. A., and Ackerman, L. V.: Cellular blue nevus. Clinicopathologic study of forty-five cases. Cancer, *21*:393-405, 1968.
57. Skov-Jensen, T., Hestrup, J., and Lambrethsen, E.: Malignant melanoma in children. Cancer, *19*:620-626, 1966.

58. Smith, J. L., Jr., and Stehlin, J. S., Jr.: Spontaneous regression of primary malignant melanomas with regional metastases. Cancer, *18*:1399-1415, 1965.
59. Southwick, H. W., Slaughter, D. P., Hinkamp, J. F., and Johnson, F.: The role of regional node dissection in the treatment of malignant melanoma. Arch. Surg., *85*:63-89, 1962.
60. Stegmaier, O. C.: Cosmetic management of nevi. J.A.M.A., *199*:917-919, 1967.
61. Stehlin, J. S., Jr., and Clark, R. L.: Melanoma of the extremities. Experiences with conventional treatment and perfusion in 339 cases. Amer. J. Surg., *110*:365-383, 1965.
62. Stehlin, J. S., Jr., Hills, W. J., and Rufino, C.: Disseminated melanoma. Biologic behavior and treatment. Arch. Surg., *94*:495-501, 1967.
63. Stehlin, J. S., Jr., Smith, J. L., Jr., and Clark, R. L.: Malignant melanoma: Diagnosis and current treatment. Surg. Clin. N. Amer., *42*:455-467, 1962.
64. Stehlin, J. S., Jr., Clark, R. L., Smith, J. L., Jr., and White, E. C.: Malignant melanoma of the extremities. Experiences with conventional therapy; a new surgical chemotherapeutic approach with regional perfusion. Cancer, *13*:55-66, 1960.
65. Stehlin, J. S., Jr., Smith, J. L., Jr., Jing, B.-S., and Shearin, D.: Melanoma of the extremities complicated by in-transit metastases. Surg. Gynec. Obstet., *122*:3-14, 1966.
66. Stout, A. P.: Observations on biopsy diagnosis of tumors. Cancer, *10*:912-921, 1957.
67. Taylor, G. W.: Unnecessarily radical surgery—an editorial. Surg. Gynec. Obstet., *93*:246-247, 1951.

The Treatment of Postsurgical Lymphedema

HARRY S. GOLDSMITH, M.D.*

In dealing with the surgical control of cancer, various complications must be accepted as the price paid for possible cure. One of the complications that can be very disabling to a patient is postsurgical lymphedema of an extremity. Particularly common is lymphedema following radical mastectomy, in which a little over one third of the patients will have what is generally described as moderate (25 per cent) or marked (10 per cent) edema of the arm.[1]

PATHOGENESIS

The basic cause of postsurgical lymphedema is lymphatic interruption resulting from the surgical removal of lymphatic tissue. This results in the backup of lymph within the distal lymphatic channels, which eventually becomes reflected in increased tissue fluid in the interstitial space. The distention of the interstitial space by this increased tissue fluid puts traction on the connective tissue fibers attached to the lymphatic capillaries. The lymphatic valves thus become incompetent and can no longer prevent the pull of gravity from exerting its downward and peripheral effect upon the lymph column. Thus, a vicious cycle of lymph stasis, interstitial fluid overload, and lymphatic valve incompetence becomes established.

TREATMENT

The aim of all surgical procedures for lymphedema has been to reestablish lymph flow. Unfortunately, however, lymphedema of a chronic nature has been a condition resistive to the many forms of surgical treatment devised for its control. Because of the large number of radical mastectomies, radical vulvectomies, and radical groin dissections performed yearly at Memorial Hospital, chronic lymphedema, in a certain

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percentage of these patients, is inevitable. These patients with chronic lymphedema stimulated our surgical research laboratory to try to develop a relatively simple procedure which might be successful in controlling postsurgical lymphedema.

An operation has been developed whereby the intact omentum, with its rich lymphatic and vascular supply, can be lengthened markedly with viability of the omental pedicle being maintained by the intact gastroepiploic vascular arcade.[3-5] The technique gives sufficient length to the omentum to allow it to be placed into any lymphedematous limb. The rationale for the operation is that the omental lymphatics will develop functional connections with the deep lymphatics of the lymphedematous extremity.

The first surgical step in omental transposition is freeing the entire omentum from the transverse colon. Following this maneuver, the surgeon removes the omentum from approximately two thirds of the greater curvature of the stomach, always being careful to protect the gastroepiploic arcade within the omental pedicle. When the omentum is to be inserted into a lymphedematous leg, a retroperitoneal tunnel is developed to just below the inguinal ligament. A counterincision is then made

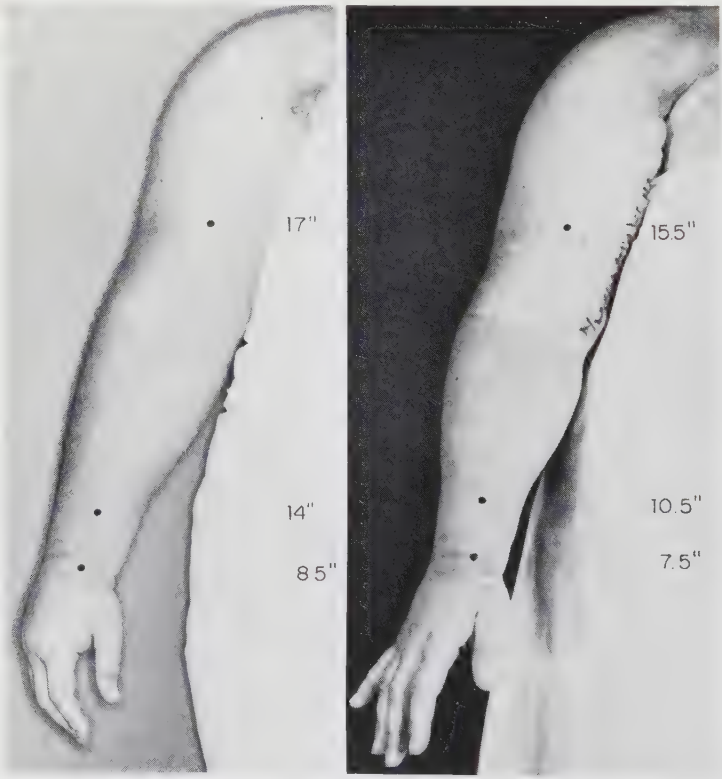

Figure 1. A decrease in the size of an extremity may appear even before sutures are removed without arm elevation.

on the anterior thigh, and thickened subcutaneous tissue and fascia are removed from the underlying thigh muscles. The omentum is then carefully pulled through the retroperitoneal tunnel and spread as an omental apron over the anterior thigh muscles.

When omental transposition is performed for lymphedema of the arm, the omentum is freed from the transverse colon and the greater curvature of the stomach as previously described and brought through a subcutaneous tunnel on the chest wall. A counterincision is then made

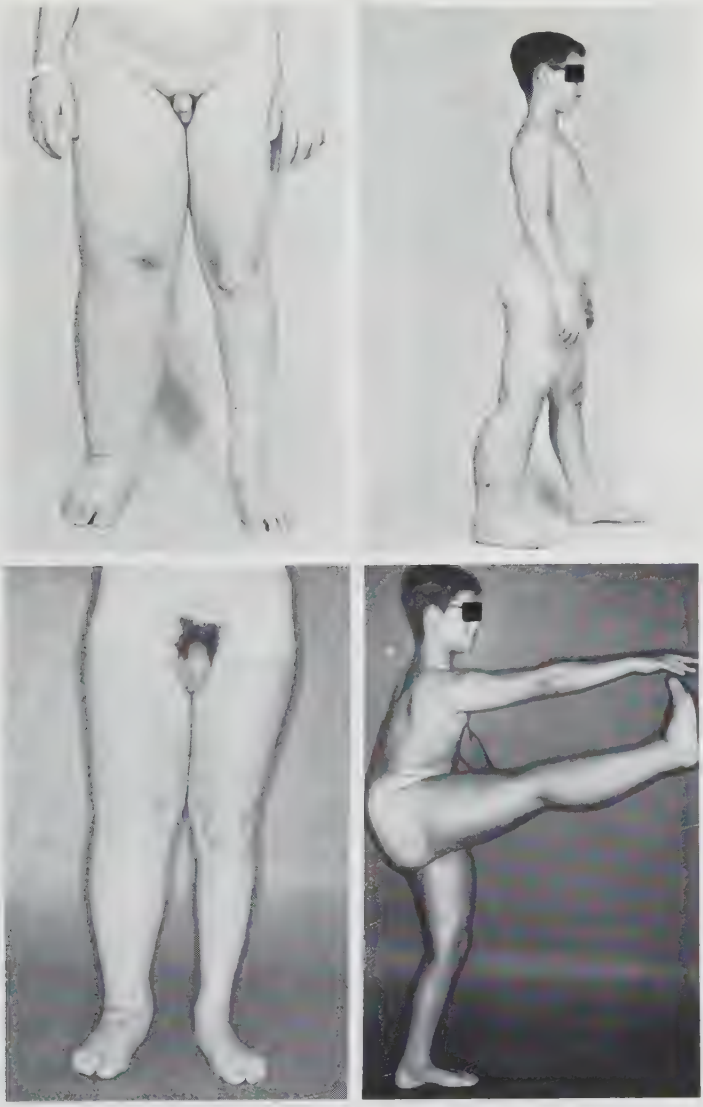

Figure 2. Improved mobility was best demonstrated in a patient with congenital lymphedema who dragged his leg preoperatively because of its increased weight. Omentum was placed into the lower leg.

Figure 3. Edema of the hand prevented this patient from writing or sewing. These activities are now possible. Patient is shown 1 year postoperatively.

on the upper arm, and thickened subcutaneous tissue and fascia are removed from the biceps muscle. The omentum is then carefully pulled through the subcutaneous tunnel on the chest wall and is laid as an omental apron on the underlying muscles of the lymphedematous arm.

RESULTS

Omental transposition has been carried out, up to the present time, on 14 patients, with satisfactory subjective and objective results being seen in 12. In one patient who demonstrated no improvement after omental transposition, subsequent omental biopsy showed radiation changes "consistent with previous x-ray therapy." Sixteen years prior to undergoing surgery for the lymphedematous condition, the patient had received x-ray therapy to lymph nodes in his groin for Hodgkin's disease and, in retrospect, his omentum must have been involved in the radiation field.

Objective improvement after omental transposition has been evaluated by the following criteria:

1. A diminution in circumferential measurements at fixed points on the lymphedematous extremity. This reduction in the size of an extremity frequently is seen early in the postoperative period (Fig. 1).
2. The complete disappearance or marked diminution in attacks of lymphangitis and cellulitis of the lymphedematous limb. Omental transposition has dramatically controlled this problem by the apparent elimination of lymph stasis.
3. Increased function of the involved extremity (Fig. 2).

4. A marked decrease in the tissue turgor of the lymphedematous limb (Fig. 3).

All but one of the patients who had been troubled preoperatively with numbness and decreasing motor function of their upper extremity noted improvement after omental transposition. It has been shown that the omentum can bring blood to an extremity.[2] This increased blood flow plus the reduction in the weight of the enlarged limb is most likely the basis for this improvement.

COMPLICATIONS

Complications occurring after omental transposition have included the following:

1. Postoperative wound separation. The space between the skin edges healed by secondary intention, and did not apparently jeopardize the patient's postoperative result (Fig. 4).

2. Two postoperative hernias, one inguinal and one Spigelian. The Spigelian hernia occurred after an attempt was made to bring the omentum out of the peritoneal cavity, several inches above the inguinal liga-

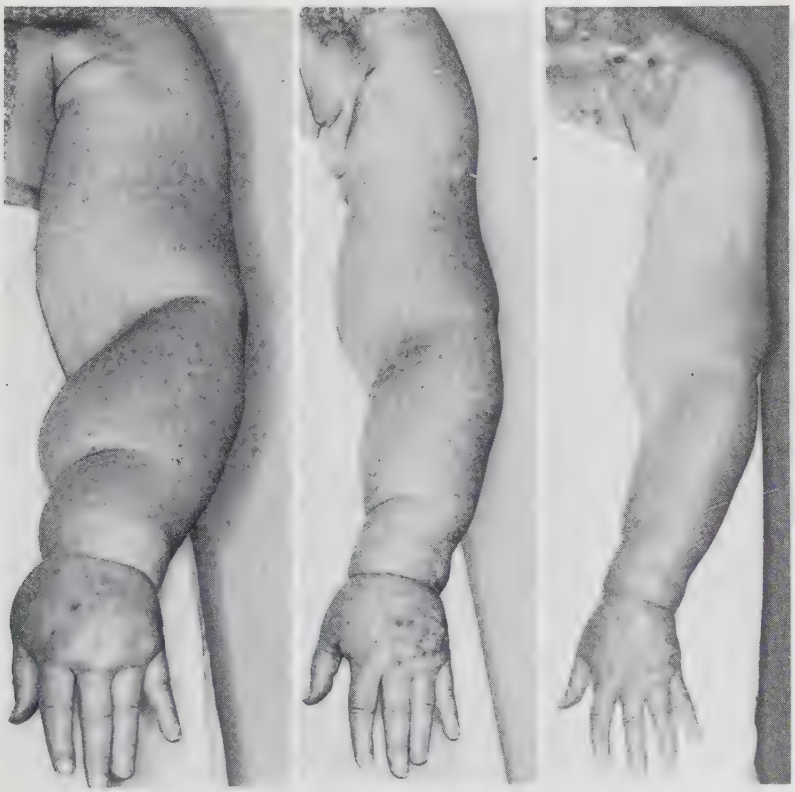

Figure 4. Composite picture of a patient: preoperatively, 12 months postoperatively, and 18 months postoperatively.

ment and immediately lateral to the rectus muscle. This method was used in order to bring omental tissue into both a lymphedematous extremity and a lymphedematous scrotum.

3. The only serious complication following the operation was in a patient with chronic lymphedema of a leg who had a previous history of thrombophlebitis. Postoperatively, she did well, and was discharged on the ninth postoperative day. She subsequently developed pulmonary embolus and small bowel obstruction, which was found to be secondary to a single adhesive band.

CONCLUSIONS

The physiologic basis for omental transposition was recently confirmed by operative demonstration that the lymphatics between a lymphedematous extremity and those of the omentum do connect and remain functional over a period of time.[6] Initial enthusiasm continues over the results seen in patients treated for chronic lymphedema by omental transposition. However, the small number of patients in this series with a follow-up of only two and a half years necessitates continued cautious optimism.

REFERENCES

1. Farrow, J. H.: Rehabilitation following radical breast surgery. Ca, *16*:222-224, 1966.
2. Goldsmith, H. S.: Omental transposition for peripheral vascular insufficiency. Rev. Surg., *24*:379-380, 1967.
3. Goldsmith, H. S., and de los Santos, R.: Omental transposition for the treatment of chronic lymphedema. Rev. Surg., *23*:303-304, 1966.
4. Goldsmith, H. S., and de los Santos, R.: Omental transposition in primary lymphedema. Surg. Gynec. Obstet., *125*:607-610, 1967.
5. Goldsmith, H. S., de los Santos, R., and Beattie, E. J., Jr.: The relief of chronic lymphedema by omental transposition. Ann. Surg., *166*:573-585, 1967.
6. Goldsmith, H. S., de los Santos, R., and Beattie, E. J., Jr.: Omental transposition in the control of chronic lymphedema. J.A.M.A., *203*:1119-1121, 1968.

Protection of Vascular Prostheses Following Radical Inguinal Excisions

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Primary or metastatic malignant neoplasms in the inguinal area may enlarge to the point where there is ulceration through the overlying skin. To remove these tumors by a wide tridimensional excision requires an en bloc resection. If the required excision entails sacrifice of the major artery, it might, on occasion, be necessary to insert a vascular prosthesis in an area of marked contamination.

The purpose of this paper is to present a one-stage technique for protecting vascular prostheses which might require insertion in an area of possible infection at the time of radical inguinal excision.

CASE REPORT

M.J., a 64-year-old man, first noted a mass in the right groin in 1953. This lesion was excised and reported as myxoliposarcoma. During the next 14 years, the patient had 14 recurrences of this tumor, all requiring resections. During the course of these various procedures, a right radical groin dissection, bilateral radical orchiectomies, and partial excision of the right pubic bone were done in the hopes of controlling his disease. The multiple procedures eventually resulted in lymphedema of his right leg.

On one occasion, an attempt was made to study the possible radiosensitivity of this tumor by directing 4000 rads from a supervoltage source to a discrete tumor in his right groin. Initially, the mass decreased in size, but once radiation therapy was terminated, immediate progression in the growth of the tumor occurred, indicating marked radioresistance. Radiation therapy was never again used in trying to control the disease.

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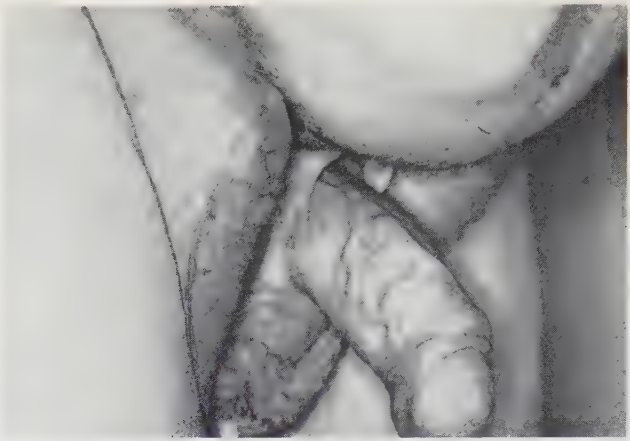

Figure 1. Oblique view of inguinal tumor.

In 1965, a 3.5 × 3 cm. lesion appeared in the midline of the lower anterior abdominal wall; it was removed and reported to be myxoliposarcoma. By May 1967, the patient had developed a large fixed irregular mass in his right groin. At surgery, the mass was described as measuring 6 × 5 × 4 inches with partial extension above and below the inguinal ligament and with fixation to the femoral vessels and deep structures. Because of the intimacy of the tumor to the major nerve and vascular structures of the leg, the operating surgeon, at that time, performed only a biopsy, which showed myxoliposarcoma.

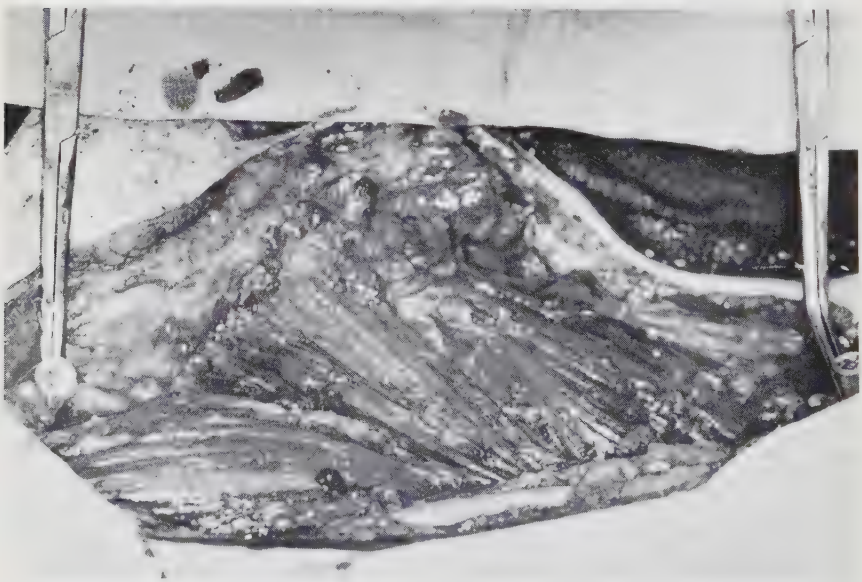

Figure 2. Operative site after radical excision of inguinal tumor. Vascular clamps on artery.

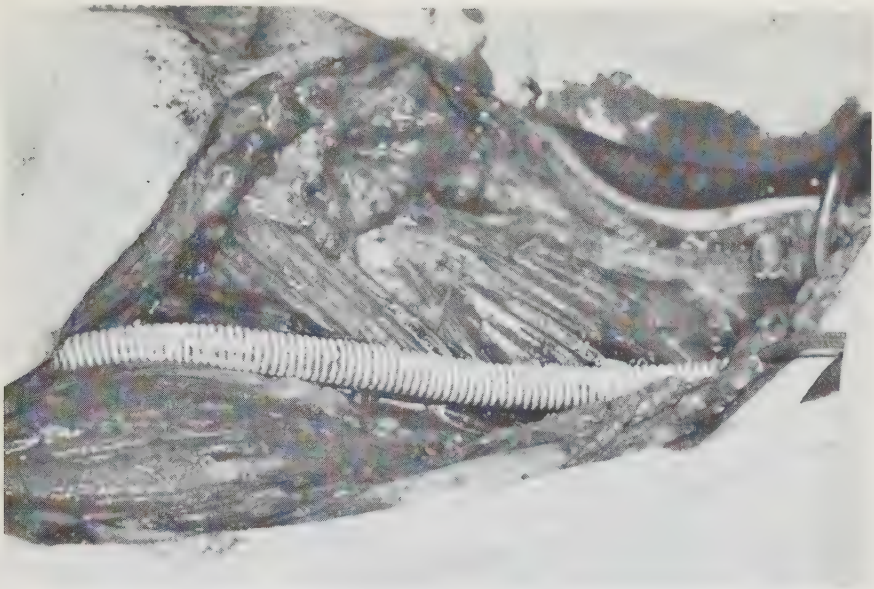

Figure 3. Dacron prosthesis used to re-establish blood flow to the leg. Note extensive dead space posterior to the graft.

During the following 6 months, the mass continued to enlarge markedly and by November 1967, the patient decided to come to Memorial Hospital for whatever surgical procedure was indicated (Fig. 1). Hemipelvectomy was considered, but because of the previous metastasis in the abdominal wall as well as the patient's marked reluctance to undergo this procedure, it was decided to attempt a very wide local excision.

A radical excision of the inguinal area was carried out, including the major nerve and vascular structures to the leg (Fig. 2). Previous surgery made autogenous vein grafting impossible, so that re-establishment of the arterial flow was accomplished by inserting a 10-inch knitted Dacron prosthesis from the lower edge of the external iliac artery to the superficial femoral artery.

After the vascular prosthesis had been inserted, it was evident that the resected rectus femoris muscle left a large dead space posterior to the vascular replacement in the adductor canal (Fig. 3). In view of the known lymphedema of the involved leg, plus the expected lymph drainage from the severed lymphatics in the operative field, it appeared inevitable that the replacement graft would be constantly bathed in lymph. In addition, covering of the vascular prosthesis was going to require extensive skin grafting, with subsequent infection being a likely possibility. Since any infection would have been nourished by the lymph fluid, it was decided to use the omentum to protect the vascular prosthesis from possible infection.

After the peritoneal cavity was entered through a low midline incision, the omentum was entirely freed from the transverse colon. Following this step, the omentum is usually removed from approximately

Figure 4. Vascular prosthesis being wrapped with intact omentum.

two thirds of the greater curvature of the stomach, leaving the gastro-epiploic arcade within the omental pedicle. This maneuver markedly lengthens the omentum so that it can be used for graft protection as far distally as the popliteal space. In the case being reported, it was

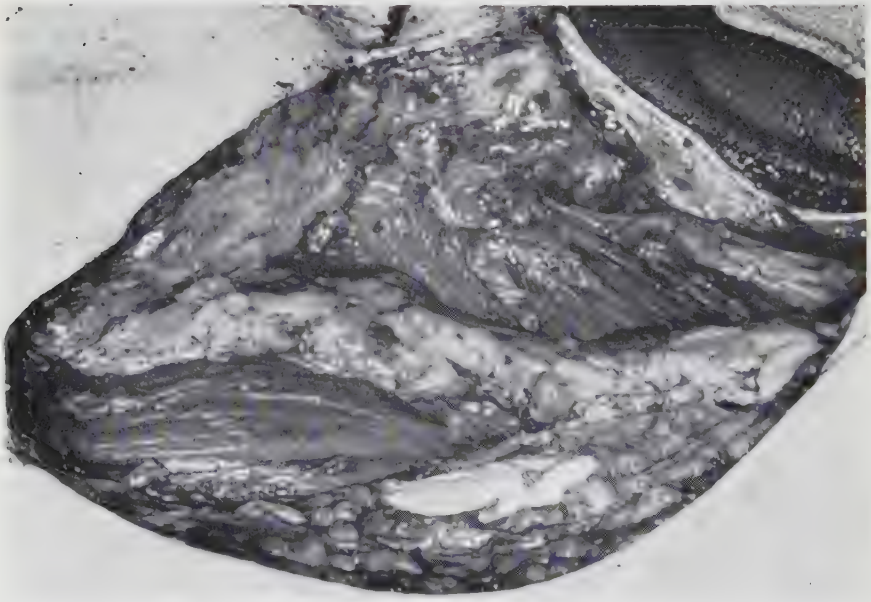

Figure 5. Omentum completely sealing vascular prosthesis and anastomoses.

Figure 6. Patient 2 months after surgery. Fifteen months postoperatively, patient continues to be clinically free of malignant disease and has good circulation in his leg.

unnecessary to remove the omenum from the greater curvature of the stomach, since sufficient omental length was obtained merely by freeing it from the transverse colon.

After the omentum had been mobilized, it was brought through a tunnel in the retroperitoneum and delivered into the leg by the technique previously reported by the authors.[2] The omentum was then completely wrapped around the vascular graft with several absorbable sutures being placed to prevent unwrapping (Figs. 4 and 5). A full-thickness skin flap was made from the lateral thigh and rotated over the prosthesis. Split-thickness grafts were taken from the opposite leg in order to cover the defect caused by this flap rotation. The patient had an uneventful postoperative course and was discharged (Fig. 6).

DISCUSSION

Radical excision of inguinal neoplasms may require excision of the major nerve, artery, and vein of the involved extremity. Removing the femoral nerve results in marked weakness of the quadriceps muscles. However, a patient can learn to adjust to this disability by walking with a stiff-leg gait, with or without crutches or a cane. If buckling of the leg

at the knee joint is a problem, braces are available which support the leg by preventing knee flexion.

Tumors that grow in the inguinal area may slowly obstruct the large veins, thereby allowing a collateral venous circulation to develop by the time of tumor excision. Even though this circulation might appear to be adequate, excision of the major venous channel of the leg can lead to various degrees of edema, which usually can be controlled with elastic stockings.

The main difficulty in a wide en bloc excision in the inguinal area is in finding a method to re-establish the arterial return to the leg. When an arterial segment is excised along with a tumor mass, a venous graft may not be available, for various reasons, for re-establishing the arterial circulation. An artificial vascular prosthesis then becomes necessary. There may be little surrounding tissue to cover the prosthesis and, frequently, the inguinal area is contaminated. This operative situation is highly conducive to the development of infection in the area surrounding the vascular graft.

Various ingenious methods have been suggested for re-establishing circulation to the leg in the presence of actual infection. Shaw and Baue[5] and Maloney and Whelan[4] have bypassed an infected aortic and iliac area by placing a prosthesis through the obturator foramen. Donahoe and associates[1] treated an ulcerated inguinal neoplasm by using a three-stage technique. They initially inserted a vascular prosthesis through the obturator foramen in order to bypass infection in the groin. Three weeks later, the tumor was resected. Two months after this excision, the defect in the inguinal area was covered with split-thickness skin grafts.

Work in our surgical research laboratory has resulted in confidence in the omentum to protect vascular prostheses from infection. A large number of dogs have had their abdominal aorta replaced with a Dacron prosthesis. Some of these vascular grafts were immediately challenged with liquid feces, whereas others were inserted in the presence of a previously developed retroperitoneal abscess. The animals who had their replacement grafts protected by omentum had a survival rate of approximately 75 per cent, as opposed to a 25 per cent survival rate in the animals without omental protection.[3] The follow-up in these animals was over a year, after which time the dogs were sacrificed. At autopsy, the omentum showed its ability to protect the individual fibers of a vascular graft and to penetrate the interstices of the fabric. This penetration was followed by endothelial proliferation within the lumen of the prosthesis (Fig. 7).

SUMMARY

A one-stage procedure is presented for the excision of large inguinal tumors requiring wide resection of surrounding structures. When an inguinal tumor requires the simultaneous excision of the major artery to the leg, a vein graft may not be available for re-establishing arterial circulation to the leg. This situation would thus require the use of an arterial replacement graft, which, on occasion, may have to be inserted in the

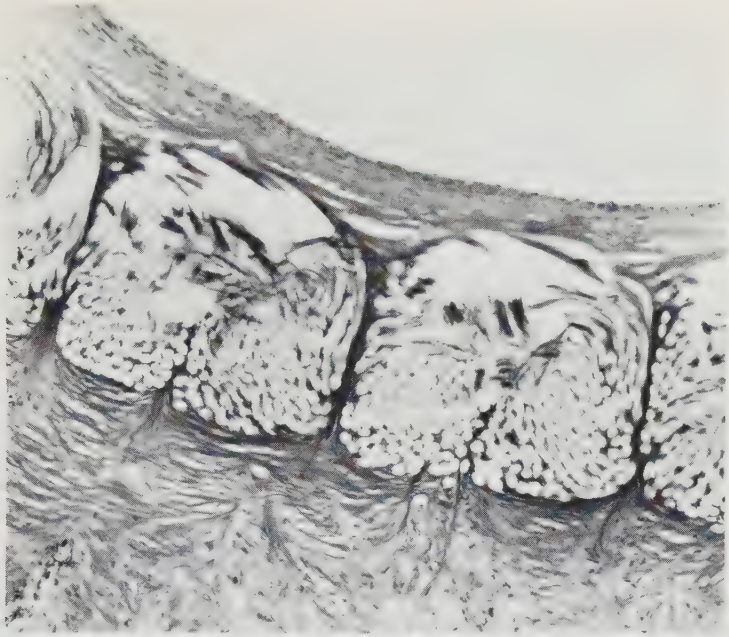

Figure 7. Photomicrograph of vascular prosthesis wrapped with omentum. Tissue seen growing between and into major threads of the fabric with envelopment of individual fibers. Observe endothelium-lined intima.

presence of actual or potential infection. The omentum appears to have the ability to protect the graft and seal it from surrounding infection. A case is presented to show the operative technique for carrying out this procedure.

REFERENCES

1. Donahoe, P. K., Froio, R. A., and Nabseth, D. C.: Obturator bypass graft in radical excision of inguinal neoplasm. Ann. Surg., *166*:147-149, 1967.
2. Goldsmith, H. S., de los Santos, R., and Beattie, E. J., Jr.: Relief of chronic lymphedema by omental transposition. Ann. Surg., *166*:573-585, 1967.
3. Goldsmith, H. S., de los Santos, R., Vanamee, P., and Beattie, E. J., Jr.: Experimental protection of vascular prostheses by omentum. Arch. Surg., *97*:872-878, 1968.
4. Maloney, W. D., and Whelan, T. J.: Use of obturator foramen in iliofemoral artery grafting. Ann. Surg., *163*:215-220, 1966.
5. Shaw, R. S., and Baue, A. E.: Management of sepsis complicating arterial reconstructive surgery. Surgery, *53*:75-86, 1963.

The Treatment of Primary and Metastatic Localized Bone Tumors by Cryosurgery

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THEODORE R. MILLER, M.D.**

The purpose of this paper is to discuss the use of cryosurgery, the application of extreme cold, as a treatment for selected localized bone tumors. Historical, theoretical, and pathologic material is presented. This article consists of a list of complications and a summary of presently conceived indications and contraindications.

HISTORICAL BACKGROUND

The first patient treated by cryosurgery, on February 10, 1964, was a 48-year-old man whose lung cancer had spread to his humerus (Fig. 1). His painful metastasis was clinically unrelieved by two courses of x-ray therapy, and we decided to attempt to freeze the lesion. The relief of arm pain was complete. We thereafter undertook a more extensive trial of cryotherapy for bone disease, and our first group of patients were those with metastatic disease.

THEORY[1]

In May 1966, Andrew A. Gage[2] produced bone necrosis in laboratory animals by wrapping a tube in a coil-like fashion around a bone. Through this tube, liquid nitrogen was circulated at −196° C. He also demonstrated subsequent bone regeneration from the periosteum and endosteum. We were also able to demonstrate such bone necrosis and subsequent regeneration in the dog. In our laboratory, trial applications of freezing were performed by the intramedullary insertion of a double-lumen probe through which liquid nitrogen was circulated. This was

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Figure 1. The first patient treated by cryosurgery (February 10, 1964) for a bone lesion was W. D., a 41-year-old man whose painful humerus metastasis was unrelieved by 4000 rads of radiation therapy. Postoperatively he was completely relieved of his pain. The alternative to therapy was palliative amputation or cordotomy, since increasing amounts of narcotics were of no avail.

also one of the methods used clinically. The difference between the area of visible ice formation in bone and the area of actual necrosis is illustrated in Figure 3*A*. Bone necrosis occurs at −21° C. or colder.[3] In our experience, this region includes not the 81 per cent that Jennings[3] predicted, but only 50 per cent of the radius of ice from the heat sink. Factors involved in the spread of freezing and subsequent necrosis are density and vascularity[3] of bone, presence or absence of a tourniquet, size and temperature of the heat sink, duration of freeze, rate of freezing, as well as thawing,[5] and the presence of cryoprotective molecules.[1] This area of cryonecrosis is based on our experimental and clinical experience as proved by subsequent biopsy, and the area is smaller than predicted by Jennings,[3] who did anticipate that clinical experience would give different amounts of necrosis (he worked with a water bath).

EQUIPMENT

1. Liquid nitrogen, temperature −196.6° C. (produced by Union Carbide) may be transported in double steel-lined thermos bottles.

2. Union Carbide–Linde CE-4 heavy duty freezing system and probes of various sizes from 2 to 20 mm. in diameter, depending on the size of the lesion and the amount of bone to be frozen.

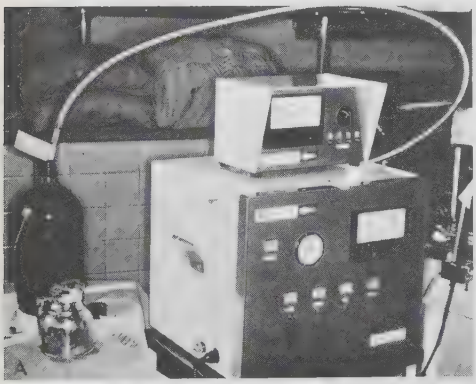
3. A tissue temperature indicator with four thermocouple attachments helps to monitor the extent and depth of the freeze.

METHOD

The plan of treatment is to reduce the temperature of the involved bone and tumor to at least −21° C.[3, 6] Freezing and thawing is done at least three times. This is best monitored by thermocouples.

For lesions projecting into soft tissue, a double-lumen probe is used. The adjacent nontumorous soft tissue is preferably not stripped from the lesion. (Neurovascular bundles should be held away.) The probe is applied at first on the surface, and repeated cryosurgical applications are made deeper and deeper into the lesion itself. The lesion then may be removed from the bone and the bone base attachment area can be frozen (Fig. 4).

A second method has been found to be useful. A thorough curettage for giant cell tumor, for example, is first performed. This usually results in a large, irregular intraosseous cavity. A stainless steel funnel is sealed into the bone opening with a moistened Gelfoam block, so that liquid nitrogen subsequently can be poured into the cavity. The cold freezes the Gelfoam block, forming a tight seal. The level of fluid nitrogen is kept high in the funnel, ensuring complete filling of the intraosseous cavity. The cavity must be suctioned between each cryosurgical application to ensure that it has not been partitioned off by blood welling up from within the bone. Because of the limitation of the zone of −21° C.



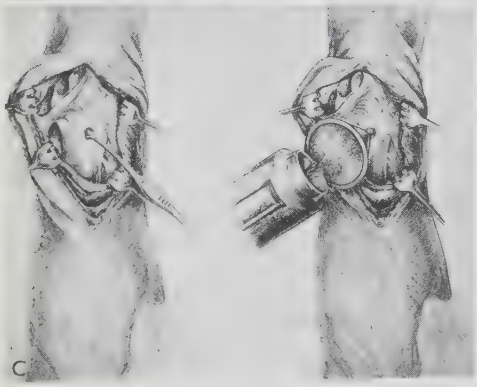


Figure 2. *A*, The "heavy freezing capability system" of Union Carbide along with its "tissue temperature indicator." The probe is being chemically sterilized. *B*, The probe method of freezing tumor bone tissue. *C*, The pouring method.

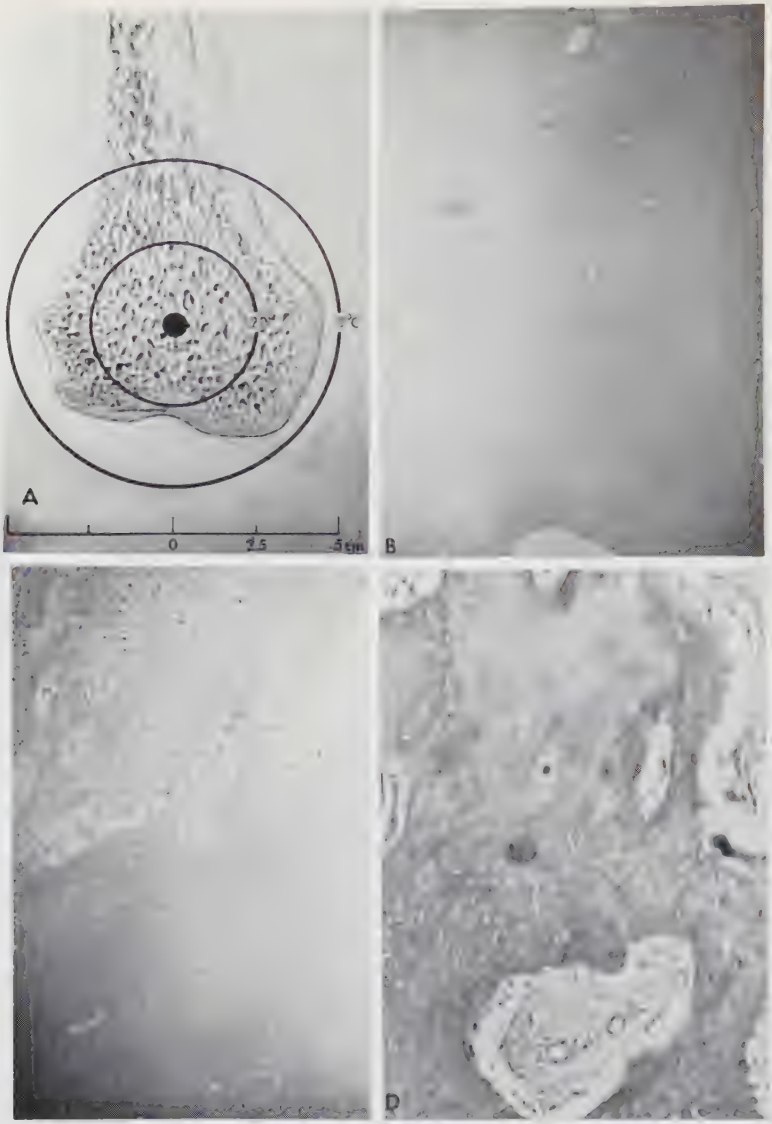


Figure 3. *A*, The range of visible ice (0° C.) and the rapid rise in temperature from the heat sink source (−180° C.). Repeated achievement of at least −20° C. must be accomplished (three times) to obtain necrosis. *B*, Necrosis of dog cortex is shown by empty lacunae. (Specimen taken 4 weeks after cryosurgery.) *C*, Periosteal new bone (nonlamellar, hypercellular) is shown developing on the osteonecrotic cortical surface in 8 weeks. *D*, Endosteal new bone.

freezing and, therefore, of necrosis (usually 1 inch), curettage must be as thorough as possible. Failure occurred in one patient because curettage was not as complete as necessary.

CLINICAL CASES AND COMPLICATIONS (Table 1)

Fifty patients were treated a total of 57 times by cryosurgery. These patients had a total of 23 recurrences before cryotherapy. After cryo-

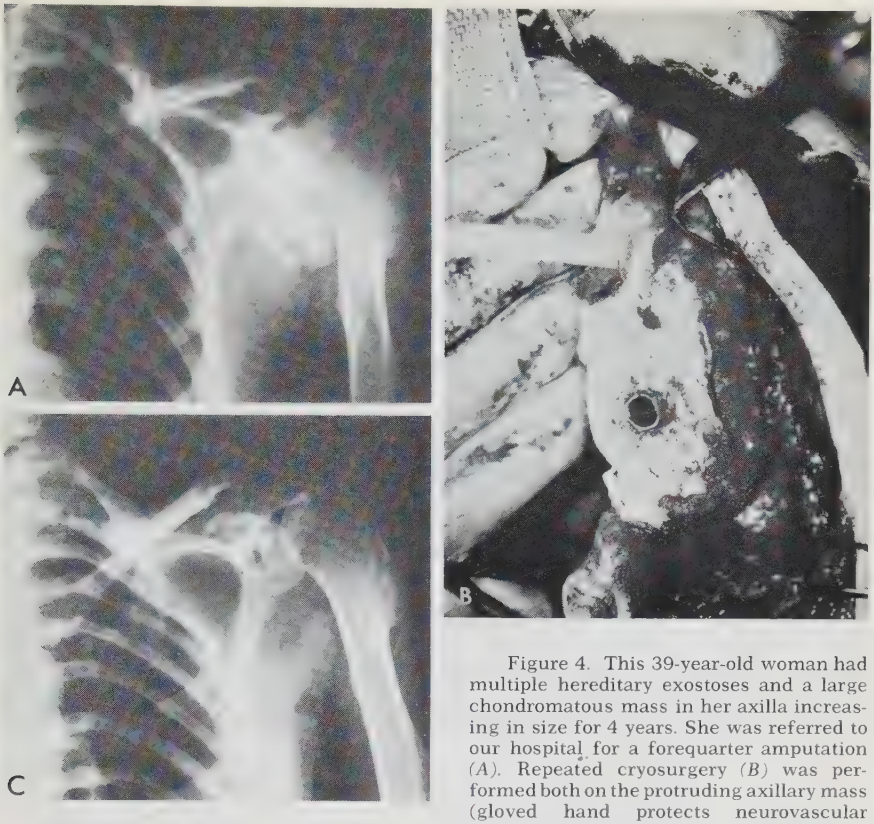


Figure 4. This 39-year-old woman had multiple hereditary exostoses and a large chondromatous mass in her axilla increasing in size for 4 years. She was referred to our hospital for a forequarter amputation (*A*). Repeated cryosurgery (*B*) was performed both on the protruding axillary mass (gloved hand protects neurovascular bundle) and on the glenoid base after the mass was osteotomized and removed. The arm now functions normally and there is no recurrence (*C*) detectable at this time (2½ years since surgery).

surgery there were seven recurrences, and cryosurgery was repeated seven times. After our initial treatment, 10 re-biopsies were done at a later date. All patients except one (E.L.) were relieved of pain following cryosurgery and remained pain-free unless recurrence developed postoperatively. Six patients treated had had preoperative fractures, and four patients suffered fractures postoperatively. Skin necrosis occurred in six patients, and two developed subsequent infections. One patient who was not operated upon personally by either author developed a 3-inch diameter skin necrosis in an arm treated for "solitary" renal cell carcinoma. Amputation was performed, because it was decided to avoid skin grafting in this patient, who had a limited life expectancy. Four patients developed transient nerve palsies which resolved spontaneously.

Recurrences probably resulted from a number of factors: (1) inadequate curettage (D.K.); (2) a lesion too big to be adequately frozen (a chordoma, H.S.); (3) inadequate number of times of freezing and thawing (J.R.); and (4) in some of the early cases, inadequate freezing by the pouring technique occurred because the technique of sealing the funnel to the lesion had not been perfected and the cavity was inadequately filled (M.d'l'P.).

Figure 5. The patient is a 55-year-old male and at this 2-year follow-up date (*B*) the recurrent giant cell tumor has remained asymptomatic following curettage, cryosurgery, and packing with homogeneous bank bone grafting. The original tumor was a lytic lesion in the lateral femoral condyle (*A*).

Figure 6. This 16-year-old girl had a painful impending fracture of the tibia (*A* and *B*). A pathologic diagnosis of fibrous dysplasia was made at open biopsy. Cryosurgery was performed and this lesion was packed with cancellous homogeneous bank bone. She now has full activity and is asymptomatic (*C*). Surgery was performed 2 years ago.

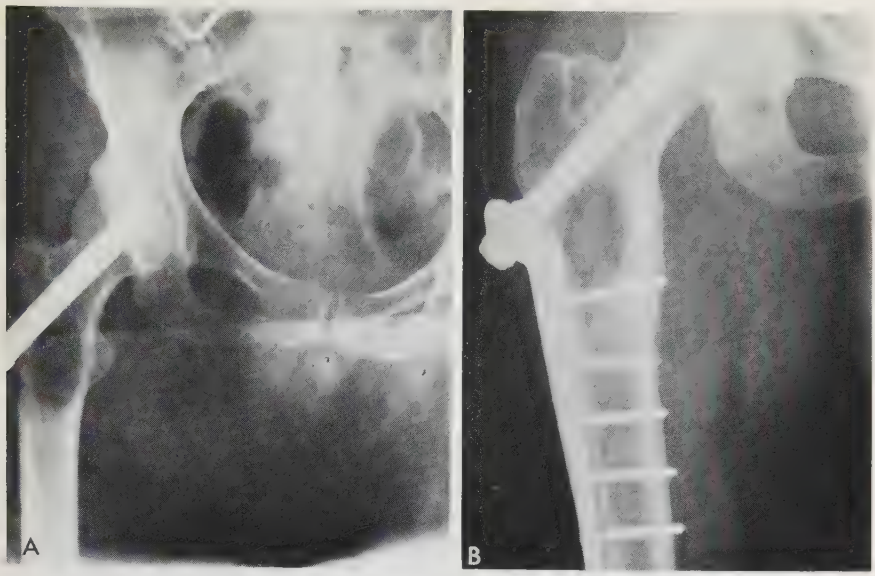


Figure 7. After removal of a renal cell carcinoma, this 53-year-old woman developed a painful "solitary" metastasis in her femur. The patient underwent cryosurgery and then nail and plate insertion. *A*, An operating room film. *B*. Productive sclerosis can be seen around the lesion 2 years after surgery. There is no local or distant extension of disease. She is pain-free and walks normally. Radiation therapy was not given.

Table 1. *Patients Treated by Cryosurgery*

PATIENT	AGE	SEX	TUMOR LOCATION	DATE OF CRYOSURGERY	DIED
			Metastatic Bone Disease		
W.D.	41	M	Carcinoma of lung metastatic to left humerus	2/10/64	July 1964
D.S.	54	F	Carcinoma of breast with pathologic fracture of hip	4/5/65	Aug. 1966
A.S.	56	M	Carcinoma of prostate with pathologic fracture of intratrochanteric region right femur (PRF)	5/20/65	2/9/67
R.M.	70	F	Renal cell carcinoma with pathologic fracture left hip (PRF)	5/20/65	6/25/65
E.L.	47	F	Carcinoma of bladder with metastases to glenoid and humerus	9/1/65	12/21/65
J.R.	63	M	Metastatic renal cell carcinoma with pathologic fracture of right distal femur (PRF)	6/8/66 (RAC)	
S.D.	56	F	Renal cell carcinoma with impending pathologic fracture of femur	July 1966	
A.G.	75	F	Metastatic renal cell carcinoma to humerus with pathologic fracture (PRF:P:NPD)	12/1/66 (RAC;N;A)	10/28/67

Table 1. *Patients Treated by Cryosurgery* (Continued)

PATIENT	AGE	SEX	TUMOR LOCATION	DATE OF CRYOSURGERY	DIED
L.B.	38	F	Metastatic myosarcoma to right iliac bone	5/23/67	7/8/68
D.E.	50	F	Adenocarcinoma of uterus to pubis (PRF)	11/6/67	
L.W.	52	M	Metastatic renal cell carcinoma to left ilium	12/28/67	
K.McG.	47	F	Metastatic ovarian carcinoma to hip with pathologic fracture (PRF)	July 1968	
K.W.	51	M	Metastatic renal cell carcinoma to left proximal femur with impending pathologic fracture	7/31/68	
			Low Grade Chondrosarcoma		
B.N.	39	F	Left anterior glenoid	3/21/66	
M.H.	51	F	Distal left humerus	1/3/67 (RAC)	
			Re-curettage and cryosurgery distal left humerus (CR:BAC)	10/10/67	
			Curettage and cryosurgery repeated (CR:BAC)	4/9/68	
L.L.	48	F	Right upper humerus	9/15/67 (POF)	
S.M.	53	F	Ilium	11/8/67	
M.M.	60	F	Distal right femur	12/21/67	
			Repeat cryosurgery	5/24/68 (CR:BAC:)	
R.A.	67	M	Right ischium	1/8/68 (RAC)	
			Repeat curettage and cryosurgery right ischium	5/7/68 (CR:BAC)	
O.J.	39	F	Distal right tibia	4/23/68 (N:PCH:P)	
F.G.	21	F	Right upper femur	5/9/68	
B.A.	54	F	Distal left femur	5/23 68	
			Aneurysmal Bone Cyst		
T.B.	14	M	Benign osteoblastoma with secondary aneurysmal bone cyst, left upper humerus (RBC)	5/21/66	
			Repeat cryosurgery left humerus	8/23/66 (CR:BAC)	
K.McC.	16	M	Aneurysmal bone cyst, right upper tibia	10/24/66	
R.R.	12	M	Aneurysmal bone cyst, distal end right humerus, secondary to unicameral bone cyst (RBC)	12/9/66	
K.H.	2	M	Benign fibromyxoma, right proximal tibia, with aneurysmal bone cyst element	7/7/66	
G.B.	15	M	Chondroblastoma (RBC), right upper humerus, with secondary aneurysmal bone cyst formation (RBC)	11/3/67	
K.M.	14	F	Aneurysmal bone cyst, left distal tibia (RBC)	12/14/67	
M.D.	51	F	Chondroblastoma, right upper tibia (RBC)	2/14/68	
D.K.	13	F	Aneurysmal bone cyst, right upper tibia, with some giant cell elements present	(BAC) 2/21/68 (RAC:POF:P)	

Table 1. *Patients Treated by Cryosurgery* (Continued)

PATIENT	AGE	SEX	TUMOR LOCATION	DATE OF CRYOSURGERY	DIED
			Giant Cell Tumor		
M.d'l'P.	18	F	Right distal femur (RBC ×3)	10/26/65 (RAC) (CR:BAC) 6/8/68 (PCH)	
M.B.	29	F	Upper tibia (RBC)	2/14/66	
L.R.	55	M	Left distal femur (RBC)	7/28/66 (N)	
B.G.	16	F	Left proximal tibia	7/25/67 (N)	
M.J.	23	F	Left distal femur	(BAC) 5/20/68 (N:SI)	
F.R.	21	F	Right middle finger, second proximal phalanx (RBC)	2/12/68 (POF)	
J.A.	66	F	Right proximal tibia (RBC ×3)	(BAC) 3/7/68 (N:SI)	
L.K.	26	M	Right proximal tibia	6/5/68 (PCH)	
R.M.	59	F	Right distal femur	8/4/68	
			Other Bone Tumors		
J.R.	15	F	Osteogenic sarcoma left distal femur Open biopsy; cryosurgery Left hip disarticulation 4/27/66	4/11/66	
C.N.	18	F	Osteogenic sarcoma left tibia Cryosurgery, then open biopsy from previously frozen area Left mid-thigh amputation 6/3/66	5/12/66	
L.D.	16	F	Fibrous dysplasia, left tibia	7/18/66	
M.V.	44	F	Hemangioma of bone (T-11)	11/25/66	
H.S.	67	M	Sacral recurrence of large chordoma	4/4/67 (P:RAC) 10/3/67 (CR:BAC)	
E.D.	43	F	Probable multiple myeloma with pathologic fracture of hip	4/6/67	
C.C.	15	F	Multifocal osteogenic sarcoma (Interscapular thoracic amputation 9/21/67) Insertion of McLaughlin nail and plate and cryosurgery to painful left greater trochanter area for palliation	3/14/68	
J.E.	5	M	Eosinophilic granuloma of left tenth rib	7/9/68	
M.A.	53	F	Multiple myeloma of left ilium	7/19/68	
C.G.	12	F	Osteogenic sarcoma, distal femur Prebiopsy cryosurgery done Amputation to follow	8/27/68	
D.S.	66	M	Multiple myeloma, humerus	7/27/68	

RBC Tumor recurrence before cryosurgery (23)
RAC Tumor recurrence after cryosurgery (7)
BAC Repeat biopsy after cryosurgery (10)
CR Cryosurgery repeated (7)
NPD Case not personally done by either author (1)
POF Postoperative fracture (4)
PRF Preoperative fracture in bone tumor (6)
N Skin necrosis (6)
NSI Skin necrosis with subsequent infection (2)
A Amputation (1)
PCH Postcryosurgery hematoma (3)
P Nerve palsy, transient (4)

INDICATIONS AND SUMMARY

At this time we do not recommend freezing a highly malignant bone tumor, since treatment must be a dependable rapid ablation to prevent distant metastasis. We do believe that freezing is indicated for a locally destructive process, especially where the alternative treatment may require at least a wide local excision or a high level of radiation therapy.

REFERENCES

1. Berggren, R., Ferraro, J., and Price, B.: A comparison of cryophylactic agents for pretreatment of preserved frozen rat skin. Cryobiology, 3:272-274, 1966.
2. Gage, A. A., Greene, J. C. W., Neiders, M. E., and Emmlings, F. G.: Freezing bone without excision. J.A.M.A. *196*:770-774, 1966.
3. Jennings, J. W., Sr.: Production and control of low temperature in cryosurgery. A.O.R.N., 7:(June), 1968.
4. Luyet, B. J., and Grell, S. M.: A study with the ultracentrifuge of the mechanism of death in frozen cells. Biodynamica, *1*:1-16, 1936.
5. Pegg, D. E.: Cryobiology: Review article. Phys. Medical Biology, *11*:209-224, 1966.
6. Rowe, A. W.: Biochemical aspects of cryo-protective agents in freezing and thawing. Cryobiology, 3:12-18, 1966.

Relative Prognostic Significance of Preoperative and Operative Findings in Pelvic Exenteration

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More than 20 years have passed since Brunschwig[10] carried out the first one-stage pelvic exenteration for pelvic cancer. Since that time, the Memorial–James Ewing Hospital group has accumulated the largest series of cases in the world for that particular procedure. Because there were no guidelines, the operation was attempted in any and all cases where the possibility existed that the disease could be cured, or reasonable palliation achieved. The necessary surgical technique had to be established initially, and then with greater experience had to be refined. The pitfalls of the operation were gradually elucidated, often by bitter experience, but in the end, the Brunschwig group learned how to do the operation so that the patient would have the maximum chance of survival and possible cure. Brunschwig must be given the credit for planning, expediting, and producing an additional operative procedure for the treatment of advanced pelvic cancer.

Now that we have learned to do the Brunschwig pelvic exenteration, the next logical step is to define when to do it, its indications as well as its contraindications. It is the purpose of this paper to set forth in an objective and dispassionate manner a set of standards for those physicians charged with caring for the unfortunate patient with advanced gynecologic cancer.

The variety and large number of cases of pelvic malignancy treated by exenteration at the Memorial–James Ewing Hospitals has given us the opportunity to evaluate the role of this operation in the treatment of this disease. This paper provides a statistical review of our results after 20 years. From these, we attempt to evolve a framework to develop the indications and contraindications for the performance of this operation.

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It will soon be apparent on appraising our figures that pelvic exenteration was undertaken in many patients in whom it was of no value. We make no apologies for this. Unless the operation was attempted on all patients whom it conceivably might have benefited, the conclusions described herein might never have been determined. In dealing with experimental therapy for advanced cancer, one must always fight man's innate feelings of discouragement and defeatism.

Until now, published reports on pelvic exenteration usually discussed the procedure in general terms or were devoted exclusively to a description of the surgical technique. This paper will go one step farther and attempt to provide a framework for the indications and contraindications, though it is impossible to supply rigid criteria for the management of each and every problem that may arise. Armed with the general principles to be outlined, it is hoped that the physician caring for women with advanced gynecologic cancer will be in a better position to make proper decisions in the management of these patients.

When indicated, pelvic exenteration stands as the only definitive treatment possible for the cure of recurrent pelvic cancer. Before attempting this procedure, however, the decision must be made as to whether the patient is operable. Based on our experience, the criteria of operability will be listed. If the disease is inoperable, there is no point in considering surgical exploration. The next step, if the patient is in the operable category, is to determine surgical resectability. This decision can be made only at the time of exploratory laparotomy. Again, we attempt to provide guidelines at this juncture.

PREOPERATIVE EVALUATION TO DETERMINE OPERABILITY

History

GENERAL HEALTH. Active pulmonary tuberculosis, untreated hyperthyroidism, cardiopulmonary problems, glaucoma.

MENTAL. Senility, psychoses, inability to accept mutilation, relationship to the family.

As in other branches of medicine, the patient's history serves to alert the responsible physician to various aspects of the problem. Although selection has been held to a minimum in the series at the Memorial–James Ewing Hospitals, in certain instances the above findings in the history served to exclude patients from operation.

STAGE OF THE ORIGINAL CANCER. The stage of the original cancer has importance in a decision on the advisability of surgery. Recurrence following stage I cancer of the cervix will undoubtedly be found to be treatable more often than that following stage IV.[39, 40] Most patients will not know the stage of their initial disease, making it necessary for the responsible physician to obtain this information from the referring doctor.

TIME ELAPSED FROM INITIAL TREATMENT TO RECURRENCE. The relationship of the time interval between treatment and recurrence or

recognition of persistence of disease is of major prognostic significance, indicating host resistance or virulence of tumor.[13] Obviously, the shorter the interval the less favorable the prognosis.[53]

Condition at the Time of Admission. Those patients referred after receiving several transfusions and requiring vaginal packing do poorly at the time of exenterative surgery, especially if they were bedridden prior to admission.[17]

Weight Loss. Weight loss is associated with progression of disease, even in the minds of the lay public. In patients presenting with recurrent cancer in whom there has been a weight loss of 15 pounds or more within 3 months (not related to diet), there has been a 40.5 per cent hospital mortality (15 of 37 patients) after treatment and very few cures.

Pain and Swelling of the Leg. The problem of pain and swelling of the leg is accepted in most instances as a contraindication to excision of the cancer.[39, 40, 42, 45] After radiation therapy, progressive leg edema and gnawing, deep-seated pain radiating down the back of the leg on the side of the pelvis where disease was clinically diagnosed, indicates disease too far advanced to be cured by present modalities of therapy. Few patients with deep-seated leg pain and leg swelling, with or without nodular permeation, have received pelvic exenteration at the Memorial–James Ewing Hospitals. However, exenteration was carried out in four such patients; one died in the hospital and survival was brief in the others.

In patients receiving preoperative irradiation followed by radical hysterectomy, swelling and edema of the leg are more difficult to evaluate, but in general this is an ominous sign associated with nonresectability.

Age. Although old age is listed as a contraindication in every series, none actually specify an age beyond which exenteration is contraindicated.[39, 40, 44] Some women show advanced metabolic and degenerative diseases at a much younger age than others. Life expectancy tables show that a woman aged 65 should reach an age of 81.2 years. Old age in itself is not a contraindication to radical surgery. However, among our patients receiving pelvic exenteration, the hospital mortality rose rapidly after age 65. Hospital mortality (death from any cause following surgery in patients who have not been discharged from the hospital in the postoperative period) among patients receiving anterior pelvic exenteration rose from zero in patients 40 years old or younger to 23 per cent in those 65 years of age or older, while in the total series hospital mortality rose from 16 per cent in patients 40 years old or younger to 38 per cent in patients 65 or older.

Any additional medical or other complicating factor added to that of old age gives an additional increase in morbidity and mortality. From 1947 to January 1963, 608 patients received pelvic exenteration for cancer of the cervix. Fifty-three patients (8.7 per cent) were 65 years of age or older. Twenty-nine had anterior and 24 total pelvic exenteration. Eleven patients lived 5 or more years (20.7 per cent), and 12 (22.6 per cent) died in the hospital. Complications in the hospital occurred in 73.6 per cent. Among 191 patients undergoing pelvic exenteration for other than cervix cancer, 23 were 65 or over (12 per cent). One patient (4.3 per

cent) lived 5 or more years and 11 (47.8 per cent) died without leaving the hospital. Twenty-one (91.3 per cent) had complications.

Physical Examination

APPEARANCE. In general the chronically ill, pale, emaciated patient who has difficulty in ambulating well by herself is a poor candidate for pelvic exenteration.

OBESITY. Obesity is always listed as a contraindication to radical surgery and it is accepted that the complication rate has a direct relationship to the weight of the patient. There is an ideal weight for height and age, reported by the various insurance companies, which serves as a guide in judging obesity. Obesity introduces technical problems, reduces the possibility for carrying out an ideal cancer operation, and increases the risk of postoperative complications – respiratory, cardiovascular, and septic. Obesity in itself may not be an absolute contraindication, but if there are any additional complicating factors the problem is quickly converted to an absolute contraindication.[39, 46] Using the above criteria of obesity as judged by the admitting physician at the Memorial – James Ewing Hospitals, 14 of 44 obese patients (31.8 per cent) receiving pelvic exenteration died without leaving the hospital.

EXTRAPELVIC EVIDENCE OF POSITIVE DISEASE. Liver enlargement secondary to disease, involved supraclavicular and inguinal lymph nodes, skin metastases, and swelling of the leg and vulva are associated with spread of disease beyond the pelvis and contraindicate pelvic exenteration.[31, 32, 39]

PELVIC FINDINGS. In general, a large lesion extending from beyond the midline to the ischial spine and characterized by nodularity, precludes the possibility of excision of the cancer.[19, 25, 38, 47]

Cancer which has spread outside the introitus indicates extrapelvic spread. If the spread is by permeation of disease the whole area is frozen, and surgical excision for cure is impossible. No patient in this series received pelvic exenteration in the presence of macroscopic disease fungating beyond the introitus. There were 11 patients who had skip metastases to the levator muscles, external urethral meatus, or perineum proper. There were no survivors among these women. All were dead in 7 days to 38 months after operation and all died with cancer present (7 days, 41 days, 4 months, 5 months, two at 6 months, two at 8 months, 11 months, 13 months, and 38 months).

SEPSIS. A large cancer complicated by sepsis may serve to contraindicate pelvic exenteration. Death from sepsis has replaced blood loss, shock, uremia, and urinary as well as small bowel fistula as the most dreaded complication of radical pelvic surgery, despite the liberal use of antibiotics. From 1947 to 1966 there were 197 deaths in the hospital among 925 patients (21.3 per cent) after pelvic exenteration for cancer of all sites. Surgical shock and sepsis were the leading causes of death in the over-all series. However, as anesthesia has improved and there are better methods of handling shock and other complications, sepsis has become the leading cause of death at present.

Laboratory Data

Blood Chemistries. There are a minimal number of laboratory procedures that are indicated prior to exploratory laparotomy.[40, 42, 54] Hemoglobin, hematocrit, urea nitrogen, creatinine, blood sugar, total protein, alkaline phosphatase, transaminase, and BSP retention must be evaluated. Other tests such as calcium, phosphorus, and electrolytes should be ordered as indicated.

Low hemoglobin and hematocrit may be associated with acute or chronic blood loss, poor nutrition, or a decreased survival time of red cells, often related to sepsis secondary to cancer.

Low serum protein and decreased blood volume indicates a state of chronic shock. Patients requiring transfusion prior to surgery generally have more complications and a low survival rate. Among patients with urea nitrogen elevated beyond 30 mg. per 100 ml., only one survived 5 years, most dying during their hospital stay. Preliminary urinary diversion has not improved the results. In each instance it has served as an indication of an advanced stage of disease.

Abnormal liver chemistries, particularly transaminase and BSP retention, have been associated with a grave prognosis.

Diabetes[15] is usually discussed under the patient's history. However, many diabetics in the present study had no prior knowledge of their disease, which was discovered only after a routine blood study had been done. Although diabetes is not a direct contraindication to radical surgery in itself, it does render the patient more brittle and labile, predisposing her to more postoperative problems. Diabetes occurred in 20 patients among 756 (2 per cent). Sixteen of the 20 received treatment 5 or more years ago and four of them lived 5 years (25 per cent)—two surviving 5 years, one for 6 years, and one for 7 years. Three of the 16 died within 24 hours, while two others died without leaving the hospital. Most of these patients had mild diabetes, which became more advanced following surgery.

X-Ray Studies. Chest x-ray, intravenous pyelogram, gastrointestinal series, and barium enema examination are important in the preoperative evaluation. The chest x-ray may reveal metastatic disease, tuberculosis, or other acute or chronic lung pathology. All are contraindications to radical pelvic surgery.[31, 39, 42]

The intravenous pyelogram has prognostic significance, as demonstrated among 503 patients operated upon between 1947 and 1956.[1] Unilateral hydronephrosis secondary to disease decreases the resectability rate by half, while in the presence of bilateral obstruction few cancers can be resected.[15–18, 38] The survival rate was 22 per cent among those with bilateral urinary tract visualization and dropped to 10 per cent in the presence of unilateral obstruction. In a group of five patients with bilateral obstruction in whom preliminary diversion was followed by pelvic exenteration, all died in the postoperative period.[51] It has been noted that if the obstruction occurs at the ureterovesical junction, the 5-year survival figures are similar to those patients in whom normal bilateral visualization is recorded. However, the survival rate falls off progressively as the blockage occurs deeper in the pelvis, reaching zero

Table 1. *Diagnosis of Recurrent Cancer of the Cervix After Treatment by Irradiation*

Symptoms
Usually none
New pain
Vaginal bleeding or staining
Swollen leg
Gnawing pain in the buttock or pelvis
Examination
Abdominal mass
Inguinal node
Pelvic mass
Ulceration or nodularity of the cervix or vagina
Asymmetry of pelvic viscera
Nodularity in the pelvis
Laboratory and clinical tests
Chest x-ray
Lymphangiogram
Pap smear
Biopsy
Intravenous pyelogram
Urea nitrogen
Creatinine
Cystoscopy, proctoscopy
Liver scan
Bone scan

when the obstruction is in the posterolateral aspect of the pelvis. Hydronephrosis is merely a stage in the progress to obstruction and represents the extent of disease.

The barium enema and gastrointestinal series are included for completeness of work-up but seldom contribute to making a decision in the management of these patients.

The electrocardiogram occasionally discloses a previously unknown myocardial insufficiency and has also directed attention to a recent infarction. An abnormal EKG does not contraindicate surgery, but may influence the timing of the indicated surgery.

PREOPERATIVE BIOPSY. Prior to exenteration recurrence can be documented in less than 20 per cent of the patients.[43] It is important to have documentation of pathology when possible. Although the problem will be discussed in more detail later, it is appropriate to point out at this time that highly anaplastic tumors[55] are associated with a high incidence of positive nodes[29, 30] as well as with spread beyond the pelvis.[16, 21, 28, 49, 52] Reticulum cell sarcoma, ovarian cancers, and lymphomas are best treated by a nonsurgical approach. Recurrent corpus cancer has a high incidence of extrapelvic spread.[8]

DIAGNOSIS OF RECURRENT CANCER OF THE CERVIX. It is difficult to diagnose recurrent cancer of the cervix.[4, 6] Recurrence in its early stage is not characterized by any specific symptom, nor is any laboratory test accurate in diagnosis. A high index of suspicion, supported by reports that more than half of the cases of cancer treated initially by radiation therapy will present with a recurrence, serves to direct attention to the

probability of recurrence in any given case. An outline is presented that will serve as a guide in evaluating patients for a possible recurrence (Table 1).

Bowel Preparation Prior to Surgical Exploration. Before surgery is undertaken the patient should be brought to the operating room in the best physical condition possible.[17, 39, 45, 54] Over and above the usual preparation the patient should have an appropriate bowel preparation, pHisoHex shower each day before surgery, permanganate douches, antibiotic suppositories or Gantrisin vaginal cream, high-calorie diet, and adequate amounts of vitamins K and C. Since sepsis has assumed a leading role in mortality during the postoperative period, careful consideration should be given to the use of a broad-spectrum antibiotic starting 2 days prior to surgery. If the patient is not physically and mentally ready for surgery, exenteration is contraindicated at that time.

RESECTABILITY

When the surgeon has determined by history, physical examination, and laboratory data that there is no contraindication to surgery, the patient is taken to the operating room for exploratory laparotomy and anticipated pelvic exenteration.[39, 40, 54] Exploratory laparotomy is not an innocuous procedure in patients with advanced cancer. Eleven of 194 (5.1 per cent) who had exploration only died in the postoperative period, while 34 others died within 3 months of the exploration, a total mortality of 23.1 per cent. A similar finding is reported for those patients explored and in whom palliative but not exenterative surgery was carried out. Among 98 patients who had palliative surgical procedures, 13 (13.4 per cent) died without leaving the hospital, while 22 others died within 3 months. The mortality within 90 days was 35 per cent, a significant mortality. Also, 97.9 per cent of patients receiving palliative nonexenterative surgery died in less than 2 years.

Upper Abdomen

Peritoneum or Free Fluid. When the abdomen is opened, the peritoneum should be evaluated by a sweep of the hand. Biopsy of any suspicious area is indicated and if any fluid is present it should be examined immediately for positive cells. A positive report indicates extrapelvic lymphatic permeation, and survival in this group is brief indeed.[54]

Visceral or Para-aortic Involvement. Positive disease involving viscera in the upper abdomen precludes the possibility of cure and the procedure should be abandoned. Careful attention should be given to the para-aortic area.[36] Occasionally, sheets and nodules of cancer may be mistaken for the bony prominence of the vertebral column.[31, 32, 51] In instances where there is a high degree of suspicion that cancer may be present in the para-aortic area (a large, anaplastic cancer that resisted initial treatment) and no nodes are palpated through the posterior peritoneum, there is justification for reflecting medially the descending colon with its mesentery, exposing the whole posterior wall of the

abdomen. Disease confirmed above the pelvic brim contraindicates radical excision regardless of where the bifurcation of the aorta begins. Among 901 patients receiving pelvic exenteration for cancer of the cervix, 19 were found to have para-aortic node metastases, 13 recurrent and 6 fresh. The exenterations were done following negative frozen section reports, which later were changed after reviewing the permanent sections. Of the group, only two lived 5 years. A review of the chart precludes confirmation of low para-aortic nodes, with more evidence indicating the location to be in the common iliac area. Cancer was present in each at the time of death. Six died in the hospital, four lived 2 months, one lived 3 months, one for 4 months, one for 6 months, two for 7 months, one for 8 months, and one lived 42 months.

Pelvis

DIFFICULTY IN ESTABLISHING PLANES OF DISSECTION. After careful evaluation of the upper abdomen, attention is turned to the pelvis in order to determine resectability. The peritoneum lateral to the infundibular ligament is incised and the ureter is retracted medially. A plane of dissection is found lateral to the external and common iliac vessels, which by careful finger dissection can be stripped from the psoas muscle and lateral pelvic wall and carried to the level of the lumbosacral plexus (sciatic plexus) to determine resectability along the lateral border of the specimen. A similar finger dissection medial to the hypogastric vessels can serve to explore the pelvic floor.[12, 39, 54] Having determined the technical possibilities of resection other contraindications should be checked.

INDECISION ABOUT INDICATION FOR RESECTION. If there is indecision on the indications for the procedure, it is better not to do it. Although it is hard to translate this statement into a mathematical formula, it follows that if the resection proves to be inordinately difficult technically the wise decision is to abandon the procedure.

SMALL INTESTINE RESECTION. The small bowel may be invaded by cancer, and the decision on resectability of the disease depends on whether it is biologic or a geographic spread.[11] Biologic spread is associated with skip metastases outside the pelvis and contraindicates exenteration. However, if the serosal surface of the small bowel has adhered to the tumor by geographic spread, reduced survival for 5 years can be anticipated, and survivors are reported. If the mesentery of the small bowel is involved the survival is brief, and no patients have survived 5 years. Forty-nine patients had small bowel resection carried out at the time of exenteration, and seven (14.2 per cent) lived 5 or more years. Six of the seven had cancer present in the serosa of the bowel. The worst prognostic sign among these patients was invasion of the mesentery of the small bowel in the presence of a positive pelvic node. None of the survivors in this series had a positive pelvic node.

BLOOD VESSEL EXCISION.[24] Blood vessels at the periphery of the pelvis are the most lateral structures that can be involved.[5] There were 55 patients among 840 with pelvic exenteration in whom excision of major blood vessels (common or external iliac arteries and veins) at the

periphery of the pelvis was carried out. There were four patients with excision of an artery alone and eight others in whom the vein was resected with the artery. All died within 30 days of surgery. In 43 patients the vein alone was excised and four lived 5 years. One had a positive node adherent to the vessel and in the other three the nodes were negative. Permeation of cancer to a major vessel at the periphery of the pelvis carried a hopeless prognosis in the study. Despite the fact that four patients survived for 5 years, in most instances in which it is necessary to excise a major vessel at the periphery of the pelvis to encompass the disease, the cancer is nonresectable.

Positive Nodes at the Periphery of the Pelvis.[18] The question is asked whether a pelvic node dissection at the time of pelvic exenteration for recurrent cancer of the cervix is prognostic or therapeutic.[16, 26, 27, 33-35, 37, 41, 43, 50, 54] Between 1947 and 1962, 85 patients presenting with recurrence following radiation therapy were found to have 148 positive nodes at the time of surgery, with four surviving 5 years (4.7 per cent). *Contralateral* positive nodes contraindicate radical excision of the pelvic viscera. Multiple nodes bunched within the same chain do not have the ominous prognosis that two involved nodes in different chains present. Eight patients proved to have multiple nodes, but the exact site of metastases was not accurately documented in each instance. All died with disease present (one surgical mortality, one at 4 months, two at 5 months, one at 6 months, two at 7 months, and one at 19 months). Among the 85 patients, 59 (69 per cent) were dead at the end of a year and 88 per cent at the end of 2 years. The finding of any additional contraindications in the presence of positive pelvic nodes is an absolute contraindication to radical pelvic surgery.[16]

Pelvic Bone Excision. Among 925 pelvic exenterations carried out between 1947 and 1965, 28 patients (3 per cent) had pelvic bone excision in addition to the exenteration as part of a planned en bloc procedure.[14] The original pathology consisted of cancer of the rectum (nine), cervical stump (one), cervix (three), vagina (three), and vulva (11), and one mixed mesodermal sarcoma of the vagina. Twenty of the 28 patients had either a primary rectal or vulvar cancer. Nine had gross disease left in at the time of radical surgery. Three among 28 patients lived 5 or more years, bone proving to be negative for cancer in each instance. Nineteen of 28 had histologic evidence of cancer in the bone at the time of microscopic examination. In those instances where the bone is excised in order to get a wide margin, a small survival may be anticipated, but in the presence of positive bone histology the excision should be abandoned.

Failure After Radical Surgical Excision

Failure following radiation or surgery is not very rewarding if treatment is carried out by the same modality of therapy that was originally employed. Among those patients in whom recurrence has followed radiation, radical pelvic exenteration can salvage about 20 per cent. However, failure of radical surgery to control the primary disease is followed by few cures even when radiation therapy is employed. When

recurrence follows primary radical surgery, additional surgery has little to offer. Undoubtedly the original surgery has removed the buffer tissue and nodes lying on muscle, fascia and blood vessels. Recurrent cancer then becomes intimately associated with these structures, negating any chance for repeat radical excision. In the series of 703 fresh cancers of the cervix treated by primary surgery, 403 patients lived 5 or more years. Only 51 patients in this series received additional pelvic exenterations, and nine (17.6 per cent) lived 5 or more years. If pelvic exenteration can be carried out following failure of initial radical surgery the results are approximately the same as in the over-all series. However, very few patients are suitable for additional curative surgery following failure of primary radical surgery.

Is Pelvic Exenteration Indicated in Untreated Cancer of the Cervix?

Should any fresh cancer of the cervix be treated initially by pelvic exenteration? Despite the good survival rate following radical surgery in the treatment of cancer of stages III and IV, the loss of bladder or rectum with urinary or fecal diversion has decreased enthusiasm for exenteration as a primary form of treatment. In general, pelvic exenteration should be reserved for those patients for whom there is no chance of cure by any other modality.

Selection of the Type of Exenteration

Not only are there contraindications to pelvic exenteration, but selection of the type of exenteration is also required.[9, 12, 13, 22, 23, 32, 37, 40, 46, 54] Between 1947 and January 1960, 317 patients received pelvic exenteration for recurrent or persistent cancer of the cervix. Only five were treated by posterior exenteration, and none of them survived 5 years. Cancer of the cervix spreading posteriorly quickly becomes adherent to the pelvic floor and also invades the venous plexus in this area. In treating recurrent cancer of the cervix it is most important to excise the vagina, thus leaving the denuded bladder and ureters, which will slough from lack of support and blood supply. The high mortality rate contraindicates posterior pelvic exenteration for the treatment of recurrent cancer of the cervix. The traditional philosophy has been to tailor the procedure to fit the needs of the patient and the extent of disease. With limited disease, a procedure of magnitude less than total pelvic exenteration ought to give a significant 5-year survival. This has not been borne out, however, among patients receiving anterior pelvic exenteration. One hundred fifteen anterior pelvic exenterations were done and only 19 patients (16.5 per cent) lived 5 or more years, while 12 (10.4 per cent) died within 30 days of surgery. A 5-year survival of 16.5 per cent indicates that the best surgical judgment was not exercised in each instance and that the procedure is indicated only in a few highly selected patients. Others such as Ingersoll report that the results with anterior pelvic exenteration have been discouraging.

Inflammatory Carcinoma

Inflammatory carcinoma is a recognized syndrome in the breast and is characterized by widespread lymphatic permeation. However, little

attention has been given to this finding in the pelvis, possibly due to the fact that observation is not as easy as in the breast. The pelvic peritoneum is injected and presents a picture not too dissimilar to that seen in early peritonitis. Although it may be invaded by bacteria, the picture is not secondary to infection but rather to extensive lymphatic permeation and carries a poor prognosis and high morbidity. In such a clinical setting it is extremely important to rule out widespread disease. Firm documentation for this observation is difficult, but its significance should be appreciated.

Incomplete Excision of Cancer

Should an exenteration be carried out if disease is left behind or even thought to be left behind? Categorically, the answer is no.[39, 40, 46, 54] There will be no palliation and the brief survival will be accompanied by high morbidity. Only when all disease is removed, but where the clinical setting indicates a reduced chance for long-term survival, can resection be justified on the basis of palliation. Between 1947 and January 1965, there were 925 pelvic exenterations carried out, 799 of them 5 or more years ago. Of the 799, 608 were done for cancer of the cervix (445 recurrences and 163 fresh cases). In this group 46 patients had known disease left in the pelvis at the time of surgery. Fourteen (30.4 per cent) died without leaving the hospital and none lived 5 years. In 53 patients disease was thought to be left in but not documented, and 18 (33.9 per cent) died without leaving the hospital. Two lived 5 years but had additional therapy. Among those patients with known disease left at the time of surgery the average survival was a little over 3 months and there was little, if any, palliation. It is a common observation that patients in whom disease is left behind at the time of surgery, or in whom it is not recognized that disease was left in, do poorly postoperatively and have a slow convalescence, characterized by ileus, low grade temperature, and lethargy without any cause being definitely determined.

Blood Loss at the Time of Resection

Blood loss bears a direct relationship to morbidity and mortality in the postoperative period.[4, 6] Prior to the time that our anesthetists warmed the blood, checked blood viscosity, corrected body pH, and monitored central venous pressure, deaths resulting from blood loss occurred in the operating room or recovery room. Now patients with major blood loss survive the operation and immediate postoperative period, but approximately the same number ultimately die in the hospital. The total number of blood units lost is revealing when equated against the hospital mortality. Among 509 patients receiving 10 units or less, 75 died in the hospital (14.7 per cent). In those receiving 10 to 15 units, 28 of 118 (23 per cent) died in the hospital, as did 32 of 69 (46.4 per cent) receiving 15 to 30 units. Two out of three receiving over 30 units of blood were hospital mortalities (66.6 per cent). One of two patients in whom blood loss was not accurately known died in the hospital. Boyan reported that the average age of those leaving the hospital after massive blood replacement was 8 years younger than of those dying in the hospital.

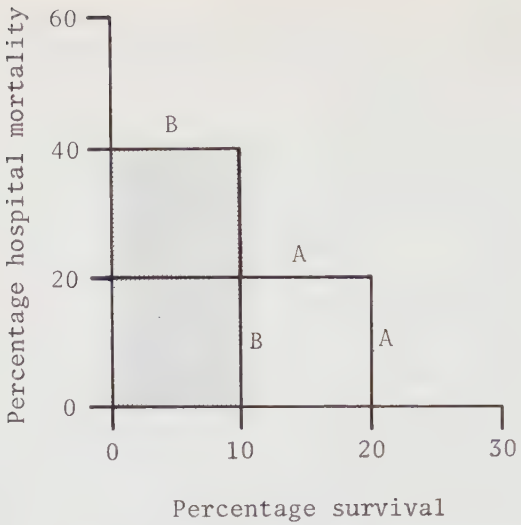

Figure 1. Guide for judging whether to do a pelvic exenteration.

MISCELLANEOUS CONSIDERATIONS

The presence of multiple contraindications increases the morbidity and mortality considerably. As an example, a 68-year-old diabetic presenting with recurrent cancer of the cervix with a nonvisualized kidney and in whom a positive node is reported at the time of exploratory laparotomy has about a 60 per cent chance of dying without leaving the hospital. In plotting a graph the point at which the survival and hospital mortality lines cross should serve as a guide for judging whether a patient should receive pelvic exenteration. As an example, in Figure 1 it is obvious that as the point of crossing of the lines moves farther to the left fewer resections should be done.

In patients with borderline indications, there is usually a high morbidity and mortality. The cost to the patient, the hospital, and the community is high and detracts from the significant role pelvic exenteration may have in treating advanced pelvic cancer if the cases are carefully chosen. Excision must be radical to overcome the disease being attacked, but the criteria for operability and resectability must not be ignored.

Cost of Hospitalization

The cost of pelvic exenteration for patients with findings suggesting contraindications is considerably higher than for those for whom no known contraindications existed. The responsible surgeon must not only know *how*, but must know *when*.

Extensive Visceral Necrosis Following Radiation Therapy

Among 794 pelvic exenterations carried out between 1947 and January 1963, there were 24 instances in which the pathologists were

unable to identify cancer, and these cases are therefore classified as "radiation necrosis."[2] In each instance the clinical impression was that of recurrent carcinoma, even though biopsy of accessible areas may have been reported as negative for cancer. Of the 24 patients, 19 were operated upon more than 5 years ago. The question that remains to be answered is whether pelvic exenteration is indicated in the presence of radiation necrosis and no evidence of cancer. Four among 19 died within 30 days of surgery, and three others died without leaving the hospital (a hospital mortality of 36.8 per cent). Eight patients lived 5 or more years (42 per cent). All patients who have had pelvic exenteration are labile, and constant supervision is essential. Ten required secondary operations, with small bowel fistulas being the most common indication. Of five patients receiving pelvic exenteration for visceral necrosis in the last 5 years, four are living.

Fortunately there has been a decrease in the total dosage of radiation administered and thus fewer patients are presenting for treatment.[37] Although pelvic exenteration may be indicated in certain select patients with visceral necrosis, a procedure of lesser magnitude should be carried out if there is a possibility of relieving symptoms and there is no evidence of cancer by biopsy.

Exenteration for Other Cancers

From September 1947 to January 1962 at the Memorial–James Ewing Hospitals, 760 patients received pelvic exenteration for 10 different disease entities as well as 1 miscellaneous group including 10 additional types of malignancy. Cancer of the cervix accounted for 76.4 per cent of these operations (Table 2). Corpus cancer is the second largest group, with 48 patients. Although corpus cancer has about the same incidence, only 48 cases were found suitable for treatment following

Table 2. *5-Year Survivors of Pelvic Exenterations at Memorial Center, September 1947 to January 1962*

	TOTAL NUMBER	LIVING 5 OR MORE YEARS	
		Number	Per Cent
Ca cervix	581	116	19.9
Ca corpus (adenoacanthoma 7)	48	7	14.5
Ca vulva (melanoma 3)	29	5	17.2
Ca rectum	27	6	22.2
Ca ovary	20	2	
Ca vagina (embryonal 1)	24	3	
Sarcoma uterus	10	2	
Ca bladder	7	1	
Mixed mesodermal	2	0	
Sarcoma botryoides	2	2	
Other	10	3	
Total	760	147*	19.3

*27 of 147 patients had positive nodes (18.3 per cent).

(Other: Granular cell myoplastoma, 1; Ca urethra, 1; adenocarcinoma tube, 1; Ca perineum, 1; liposarcoma, 1; leiomyosarcoma bladder, 1; leiomyosarcoma cervix, 1; sarcoma prostate, 1; fibrosarcoma, 1; reticulum cell sarcoma cervix, 1.)

recurrence of tumor, while 581 cancers of the cervix were found suitable for treatment.[8] The clinical syndrome characteristic of patients with corpus cancer suggests the presence of endocrinopathy. These patients are usually obese, hypertensive, hirsute, and infertile; they have menstrual problems and delayed menopause and are usually 10 years older than patients with cancer of the cervix. The medical complications plus the older age of these patients is considered by the majority of the profession to contraindicate radical pelvic surgery. The added finding reported by Hendricksen and Javert on the direct and in certain instances the early spread of cancer to the aortic chain has served to discourage a radical surgical attack. Seventy-five per cent of the patients treated for recurrent corpus cancer died during the first year after receiving pelvic exenteration, usually with cancer present.

Twenty-nine patients received pelvic exenteration to encompass recurrent cancer of the vulva, and five lived 5 or more years. Fourteen patients died in the hospital, six of whom had cancer at the time of death. Twelve of the 29 died with cancer present. In very carefully selected cases pelvic exenteration has a place in the treatment of recurrent cancer of the vulva.[7]

Cancer of the ovary[3] is characterized by its wide dissemination over peritoneal surfaces of the pelvis, upper abdomen, and omentum, and the frequent involvement of both ovaries, either as spread from the one primarily involved or as bilateral primary growths. The tendency for rapid extension to the upper abdomen, on theoretical grounds, contraindicates radical surgery. Twenty patients received pelvic exenteration for ovarian cancer. All were selected by nature, as evidenced by the fact that all survived from more than 1 year to 13 years from the initial therapy to the diagnosis of recurrence. In each instance only those patients were operated upon whose neoplasms were macroscopically confined to the pelvis and macroscopically completely excisable. Two survived 5 or more years, while the others died with carcinomatosis. Patients with advanced recurrent ovarian cancer are an unfavorable group for pelvic exenteration, and except in extremely rare instances fall into the group for whom it is contraindicated.

In addition 55 other patients had 15 different types of malignant tumors. Eleven survived 5 years. In general many of the patients had sarcomas, which are associated with a high incidence of blood-borne metastases.

In summary it can be stated that the natural history of cancer of the cervix permits a radical surgical attack by pelvic exenteration, while all the other different malignant tumors listed lend themselves to a radical surgical attack only if they do not have their usual method of spread.

CONCLUSIONS

Based upon our experience the following conclusions must be reached:

Absolute Contraindications to Surgery for Cure

Metastasis outside the pelvis (lung; supraclavicular, inguinal, and para-aortic nodes; peritoneum) or positive cells in peritoneal fluid

Visceral spread in the upper abdomen
Psychoses
Borderline cardiopulmonary reserve
Skip metastases to the small bowel
Skin metastases
Bilateral ureteral obstruction secondary to disease
Bedridden for more than 1 month from the cancer or its complications
Excessive weight loss from the contemplated exenteration
Unilateral ureteral obstruction in the posterior lateral pelvis
Technical inability to remove all disease
For palliation with known disease left behind
Permeation of disease to blood vessels at the periphery of the pelvis
Positive disease involving bone
Sepsis
Multiple contraindications present
Cancer that has broken through the serosa of the uterus
Bilateral or multiple positive nodes in different chains
Reticulum cell sarcoma or lymphoma
Inadequate hospital facilities
Lack of physician ability to cope with any and all complications

Relative Contraindications for Cure

Obesity
Over age 65
Question of being able to surgically excise all the disease
Multiple positive nodes after radiation failure
Microscopic evidence of blood vessel invasion at the primary site of cancer
Indecision on whether the patient should have exenteration
Difficulty in mobilizing the specimen
Ovarian cancer
Radiation necrosis (absence of positive biopsy)
Sarcomas
Active pulmonary tuberculosis

Judgment Decision

Big, bulky tumor
Anaplasia of tumor
Small cell carcinoma
Localized abscess in pelvis
Persistence of disease after adequate initial treatment
Lateral spread especially heading toward the ischial spine
Indication from preliminary mobilization of the specimen that blood loss will be excessive
Previously untreated cancer of the cervix
Procedure is too difficult to do
Hospital mortality surpasses the anticipated survival

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REFERENCES

1. Barber, H. R. K., Roberts, S., and Brunschwig, A.: Prognostic significance of the preoperative non-visualizing kidney in patients receiving pelvic exenteration. Cancer, *16*:1674, 1963.
2. Barber, H. R. K., and Brunschwig, A.: Pelvic exenteration for extensive necrosis following radiation therapy for gynecologic cancer. Obstet. Gynec., *25*:575, 1965.
3. Barber, H. R. K., and Brunschwig, A.: Pelvic exenteration for advanced and recurrent ovarian cancer. Surgery, *58*:935, 1965.
4. Barber, H. R. K., and Brunschwig, A.: Results of the surgical treatment of recurrent cancer of the cervix. *In* Lewis, G. C., Jr., Wentz, W. B., and Jaffe, R. M., eds.: New Concepts in Gynecological Oncology. Philadelphia, F. A. Davis Co., 1966, p. 145.
5. Barber, H. R. K., and Brunschwig, A.: Excision of major blood vessels at the periphery of the pelvis in major surgery. Surgery, *62*:426, 1967.
6. Barber, H. R. K.: Results of surgical treatment of cancer of the cervix at the Memorial–James Ewing Hospitals, New York. *In* Marcus, S., and Marcus, C., eds.: Advances in Obstetrics and Gynecology. Baltimore, The Williams & Wilkins Co., 1967, Vol. 1, p. 622.
7. Barber, H. R. K., Brunschwig, A., and Mangioni, C.: Advanced cancer of the vulva and vagina, treated by anterior and total pelvic exenteration 1947–1962 at the Memorial–James Ewing Hospitals. Cancer, *22*:949, 1968.
8. Barber, H. R. K., and Brunschwig, A.: Treatment of recurrent corpus cancer by anterior and total pelvic exenteration at the Memorial–James Ewing Hospitals, 1947 through 1962. Ann. Obstet. Gynec., *4*:219, 1968.
9. Bricker, E. M., and Modlin, J.: Role of pelvic exenteration. Surgery, *30*:76, 1951.
10. Brunschwig, A.: Complete excision of pelvic viscera for advanced carcinoma. Cancer, *1*:177, 1948.
11. Brunschwig, A., and Barber, H. R. K.: Extended pelvic exenteration for advanced cancer of the cervix. Long survivals following added resection of involved small bowel. Cancer, *17*:1267, 1964.
12. Brunschwig, A.: What are the indications and results of pelvic exenteration? J.A.M.A., *194*:274, 1965.
13. Brunschwig, A.: Surgical treatment of carcinoma of the cervix, recurrent after irradiation or combination of irradiation and surgery. Amer. J. Roentgenol., *99*:365, 1967.
14. Brunschwig, A., and Barber, H. R. K.: Pelvic exenteration combined with segments of bony pelvis. Surgery, in press.
15. Brunschwig, A.: L'Exenteration pelvienne. Paris, Masson et Cie., 1964, p. 55.
16. Cherry, C. P., and Glucksmann, A.: Lymphatic embolism and lymph node metastases in cancers of the vulva and uterine cervix. Cancer, *8*:564, 1955.
17. Cox, E. F., Ketchum, A. S., Villa Santa, U., and Mumford, R. S.: Patient evaluation for pelvic exenteration. Amer. Surg., *30*:574, 1964.
18. Dearing, R.: A study of the renal tract in carcinoma of the cervix. J. Obst. Gynaec. Brit. Emp., *60*:165-174, 1953.
19. Ellis, F.: The dose-time relationship in radiotherapy. Brit. J. Radiol., *36*:153, 1963.
20. Fletcher, G. H., Rutledge, F. N., and Chan, P. M.: Policies of treatment in cancer of the cervix uteri. Amer. J. Roentgenol., *87*:6, 1962.
21. Friedell, G. H., and Graham, J. B.: Regional lymph node involvement in small carcinoma of the cervix. Surg. Gynec. Obstet., *108*:513, 1959.
22. Friedell, G. H., Cesare, F., and Parsons, L.: Surgical treatment of cancer of the cervix recurring after primary irradiation therapy. New Eng. J. Med., *264*:781, 1961.
23. Friedell, G. H., and Parsons, L.: The spread of cancer of the uterine cervix as seen in giant histological sections. Cancer, *14*:42, 1961.
24. Friedell, G. H., and Parsons, L.: Blood vessel invasion in cancer of the cervix. Cancer, *15*:1269, 1962.
25. Friedell, G. H.: Cancer of the cervix–A Selection Review. *In* Sommers, S. C., ed.: Pathology Annual 1966. New York, Appleton-Century-Crofts Division of Meredith Publishing Co., p. 48.
26. Graham, J. B., and Graham, R. M.: The curability of regional lymph node metastases in cancer of the uterine cervix. Surg. Gynec. Obstet., *100*:149-155, 1955.
27. Graham, J. B., Sotto, L. S., and Paloncek, F. P.: Carcinoma of the Cervix. Philadelphia, W. B. Saunders Co., 1962.

28. Gusberg, S. B., Fisk, S. A., and Ym-Ying Wang: Growth pattern of cervical cancer. Obstet. Gynec., 2:557, 1953.
29. Herovici, C. A.: Polychrome stain for differentiating precollagen from collagen. Stain Techn., 38:204, 1963.
30. Herovici, C. A.: Study of reaction of connective tissue in malignant tumors of the uterine cervix. Neoplasm. (Bratisl.), *11*:225, 1964.
31. Ingersoll, F. M., and Ulfelder, H.: Pelvic exenteration for carcinoma of the cervix. New Eng. J. Med., 274:648, 1966.
32. Ingersoll, F. M.: Pelvic exenteration for carcinoma of the cervix. Ob. Gyn. Digest, *10*:49, 1968.
33. Inguilla, W., and Cosmi, E. V.: Pelvic exenteration for advanced carcinoma of the cervix. Amer. J. Obstet. Gynec., *99*:1083, 1968.
34. Jones, H. W., Jr.: Surgical treatment of carcinoma of the cervix recurrent after irradiation or combination of irradiation and surgery (editorial comment). Obstet. Gynec. Survey, 22:674, 1967.
35. Jones, H. W., Jr.: Pelvic lymphadenectomy as an adjunct to radiation therapy in the treatment for cancer of the cervix (editorial comment). Obstet. Gynec. Survey, 20:840, 1965.
36. Kelly, J. W. M., Parsons, L., Friedell, G. H., and Sommers, S. C.: A pathologic study in 55 autopsies after radical surgery for cancer of the cervix. Surg. Gynec. Obstet., *110*:423, 1960.
37. Kiselow, M., Butcher, H. R., Jr., and Bricker, E. M.: Results of the radical surgical treatment of advanced pelvic cancer: A 15 year study. Ann. Surg., *166*:428, 1967.
38. Lange, P.: Clinical and histological studies on cervical carcinoma. Acta Path. Microbiol. Scandinav., Vol. 50, Supp. 14, 1960, p. 143.
39. Mattingly, R. F.: Indications, contraindications and method of total pelvic exenteration. Oncology, *21*:241-259, 1967.
40. Mattingly, R. F.: Total pelvic evisceration. Clin. Obstet. Gynec., 8:705, 1965.
41. McClure-Brown, J. C.: Pathology and treatment of malignant glandular metastases of the lateral pelvic wall (discussion). J. Obst. Gynaec. Brit. Emp., *67*:724, 1960.
42. Mikuta, J. J.: Pelvic exenteration in carcinoma of the cervix, a review of the literature. Amer. J. Med. Sci., 236:797, 1958.
43. Munnell, E.: Can recurrent cervical carcinoma be successfully managed? J.A.M.A., *194*:275, 1965.
44. O'Leary, J. A., and Symmonds, R. E.: Radical pelvic operations in the geriatric patient. A 15 year review of 133 cases. Obstet. Gynec., 28:745, 1966.
45. Parsons, L., and Bell, J. W.: Evaluation of pelvic exenteration operation Cancer, 3:205, 1950.
46. Parsons, L.: Pelvic exenteration. Clin. Obstet. Gynec., 2:1151, 1959.
47. Parsons, L., Cesare, F., and Friedell, G. H.: Primary sugrical treatment of invasive cancer of the cervix. Surg. Gynec. Obstet., *109*:279, 1959.
48. Parsons, L., and Friedell, G.: The evaluation of pelvic lymphadenectomy in the treatment of cervical cancer. *In* Meigs, J., and Sturgis, S., eds.: Progress in Gynecology. New York, Grune & Stratton, Inc., 1963, Vol. IV, p. 445.
49. Reagan, J. W., Hamonic, M. J., and Wentz, W. B.: Analytical study of the cells in cervical squamous cell cancer. Lab. Invest., 6:241, 1957.
50. Rutledge, F., and Burns, B.: Pelvic exenteration. Amer. J. Obstet. Gynec., *91*:692, 1965.
51. Schewe, E. J., and Sala, J. M.: Bilateral ureteral obstruction complicating the treatment of cancer of the cervix. Amer. J. Roentgenol., *81*:125-129, 1959.
52. Stallworthy, J.: Radical surgery following radiation treatment. Ann. Roy. Coll. Surg., *34*:161, 1964.
53. Truelsen, F.: Cancer of the Uterine Cervix, A Report of 2918 Cases. London, H. D. Lewis & Co., Ltd., 1949.
54. Ulfelder, H.: Extended radical surgery for recurrent and advanced cervical cancer. Clin. Obstet. Gynec., *10*:940, 1967.
55. Wentz, W. B.: Histologic grade and survival in cervical cancer. Obstet. Gynec., *18*:412, 1961.

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